VOLUME 63 • FEBRUARY 1957 • NUMBER 2

PATHOLOGY

A Periodical Devoted to General and Experimental Pathology

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David Auld

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Checks, money orders, and drafts should be made payable to the American Medical Association, 535 North Dearborn Street, Chicago 10.

AMERICAN MEDICAL ASSOCIATION Publication

Published monthly by the AMERICAN MEDICAL ASSOCIATION. Editorial and Circulation Offices: 535 North Dearborn Street, Chicago 10, Illinois. Publication Office: Thompson Lane, Box 539, Nashville 1, Tennessee. Change of Address: Notice to the circulation office should state whether or not change is permanent and should include the old address. Six weeks' notice is required to effect a change of address. Second-class mail privileges authorized at Nashville, Tenn., Aug. 6, 1956.

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Pathology of the Heart in the Carcinoid Syndrome

A Comparative Study

RICHARD A. MacDONALD, M.D., and STANLEY L. ROBBINS, M.D., Boston

More than three years have now elapsed since attention was first called to an unusual association of valvular disease of the right side of the heart with widely metastatic carcinoid tumor (argentaffinoma) of the gastrointestinal tract.[1] Since that time the clinical [2] and laboratory [3] features of what has come to be known as the carcinoid syndrome continue to be subjects of unusual attention, and approximately 62 acceptable cases have been reported.[1-30] The histologic changes in the heart valves in this condition, however, have not been extensively studied, despite the fact that they are one of the most distinctive features. The purpose of the present paper is to set forth the results of a comparative microscopic study of the heart and valves in the carcinoid syndrome, contrasting the findings in these cases with the cardiac changes found in congenital, degenerative, infectious, and "collagen" diseases.

Review

A recent article published from this laboratory [4] has reviewed the historical, clinical, and pathologic features of carcinoid tumors in general, and cases of the carcinoid syndrome, so that the present review is concerned chiefly with the cardiac findings. Among 58 reported cases, excluding the 4 described from this laboratory, approximately 20 included a description of the heart in sufficient detail for our purposes; these cases are briefly reviewed.

In the original article calling attention to the association of heart changes with metastatic carcinoid tumor, Isler and Hedinger [1] reported three cases. All had tricuspid and pulmonic valve stenosis, with increased vascularity of the cusps and a covering of collagenous and hyaline tissue. The mitral valve and the left auricle were thickened in one of these cases, raising the question of previous rheumatic inflammation. In two cases reviewed by Thorson and co-workers [2] there was pulmonic stenosis, with an associated tricuspid dilatation in one and an isolated tricuspid stenosis in the other. In one tricuspid valve there was an acute inflammation, with round cells. Hedinger and Gloor [17] subsequently reported another case of the syndrome in which there was both tricuspid and pulmonic valve stenosis; a peculiar tissue, described as cartilaginous in appearance, was deposited upon the endocardium of the right ventricle and upon the valves of the right side of the heart. A detailed description, notable for its early date, was made by Millman [22] in reporting one case. Tricuspid and pulmonic stenosis were present, and in both valves there was found a dense fibrous and collagenous tissue. "Evidence of a previous inflammatory

Submitted for publication Sept. 10, 1956.

From the Mallory Institute of Pathology, Boston City Hospital.

This work was aided by a grant from the Greater Boston Chapter of the Massachusets Heart Association.

lesion was seen at the rings of the tricuspid and pulmonary valves as manifested by new blood vessels and occasional round cell infiltrations." Branwood and Bain [7] described one case in which there was thickening of the tricuspid valve and pulmonic stenosis due to dense fibrocollagenous thickening. Bean and co-workers [5] reported two cases in which valves of the left side of the heart, as well as those of the right side, were affected. It is not possible, however, from the brief descriptions given in their report to exclude rheumatic involvement. In both instances all four valves were thickened, with a "valvulitis" in one of the cases. Jenkins and Butcher [19] gave a gross description of the heart in one case in which pulmonic stenosis with tricuspid dilatation was present. Olesen [24] reported two autopsied cases, in one of which there was pulmonic and tricuspid stenosis, in the other an isolated tricuspid stenosis. The pulmonic and tricuspid valves were noted to be covered by a relatively acellular hyaline tissue. Spain [30] reported 26 cases of carcinoid tumor, not all as examples of the syndrome; 4, or possibly 5, might be considered to belong in the group under discussion. He noted a fibrosis in the endocardium beneath the pulmonic valve ring and stated that advanced valvular changes were not necessarily limited to patients with extensive hepatic metastases. The latter observation, however, is in conflict with all cases so far reported in which there has been anatomic documentation of carcinoid tumor associated with right-side heart valve lesions.

McKusick [20] presented an unusual case with patent foramen ovale and involvement of all four valves of the heart. In addition to the published details, one of us (R. A. M.) has had the opportunity of reviewing slides from this case, through the courtesy of Dr. V. A. McKusick. The striking feature of this case was the presence, in addition to "cartilage-like fibrous scarring of the pulmonic valve," of mononuclear-cell infiltration of the valve cusps, interpreted as an inflammatory process showing continuing activity. Eyler, Tesluk, and Drake [12] presented an interesting pathologic study in reporting one case. Pulmonic stenosis was present, with marked endocardial thickening of the right auricle due to the deposition of a bland fibrous tissue upon the endocardium. The fibrous tissue was noted to be without elastic fibrils, as demonstrated by the elastica stain. Horsley and Prec [18] presented one case in which there was pulmonic stenosis and tricuspid valve thickening by fibrous tissue.

To summarize the reported cases, the pulmonic and tricuspid valves have been those chiefly affected, to the exclusion for the most part of the mitral and aortic valves. Grossly, a pearly-gray thickening of the pulmonic and tricuspid valve cusps has been noted, binding the edges of the cusps together in many cases, and causing stenosis and occasionally regurgitation. Hypertrophy of the right ventricle has often been noted, and in cases where the pulmonic valve has been stenotic while the tricuspid valve has been relatively unaffected, the tricuspid valve has undergone dilatation. The fibrous process has been found to involve the right auricular and ventricular endocardium, and in some cases the chordae tendineae of the tricuspid valve as well. Histologically a fibrocollagenous substance with relatively scant cellularity has been found on the affected valves and endocardium. Many workers have not found evidence of inflammatory-cell activity, but in a few cases this has been noted. Attention is drawn to descriptions of inflammatory cells in two of the several cases reviewed by Thorson and co-workers,[2] in one case reported by Millman,[22] and in one case reported by McKusick.[20] Plasma cells and lymphocytes were found in the case described by Eyler, Tesluk, and Drake,[12] and in one of the cases reported by Bean and co-workers [5] there was noted a "valvulitis."

Material and Methods

The material with which this study was made consisted of heart preparations from approximately 280 cases of the types noted.

1. Sections of the heart were studied from 44 patients with gastrointestinal carcinoid tumor. These were separated into groups on the basis of the extent to which the tumor had metastasized. Nine patients had liver metastases, and, of these, three had acquired valvular lesions of the right side of the heart. In two of these three patients all four heart valves were available, while in the third patient only the pulmonic and mitral valves were available. Several special stains were used; in general the most useful were the phloxine-methylene blue and the elastica stain. Sections of valves from two of the other six patients with liver metastases were available; in the remainder sections of heart showing endocardium were studied. The 35 cases of carcinoid tumor without distant metastases did not have gross valve involvement; they were divided as follows: Fourteen were small tumors localized to the submucosa of the bowel. Of these, left and right side heart valves were available in three cases. Eleven were of tumor growing only into muscle coats of the bowel wall; left and right side heart valves were available in five cases. Ten were of tumor that had spread as far as regional lymph nodes; valves from the right and left sides of the heart were available in five cases.

2. As a relative control group, the hearts from 33 selected autopsies performed by one of us (R. A. M.) were studied. The cases ranged with respect to age from newborn infants to patients 88 years of age and were chosen in part to show the valves of young persons, but chiefly were cases showing some gross degree of thickening or distortion of the leaflets.

3. Three cases of congenital pulmonic stenosis were studied; the pulmonic valves were available in two cases, and all four valves in the third case.

4. The changes in rheumatic heart disease were reviewed, using sections of the heart from 104 cases. Thirty-five were sections of the left auricular appendage obtained during surgical procedures; the remaining 69 were of heart valves obtained at autopsy from patients with deforming rheumatic valvular disease or with active rheumatic fever.

5. Heart valves with both bacterial and nonbacterial thrombotic endocarditis were reviewed, drawn from material previously used in a study of nonbacterial thrombotic endocarditis.

6. Sections of heart were studied in cases of "collagen" diseases. These were 12 cases of disseminated lupus erythematosus, of which heart valves were available in 2 cases; 9 cases of periarteritis nodosa, of which valves were available in 2 cases; 2 cases of scleroderma, in 1 of which heart valves were available, and 1 case of dermatomyositis, in which sections of heart and endocardium were studied.

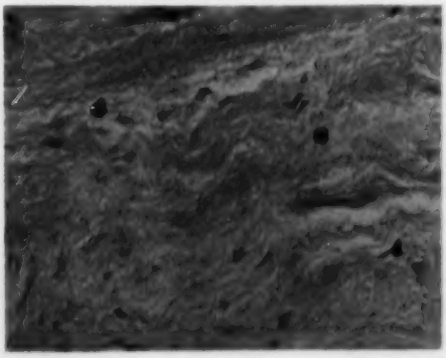
7. Two cases of congenital fibroelastosis were available in which the endocardial changes were reviewed. Heart sections were studied in two other conditions: thrombotic thrombocytopenic purpura, in three cases, and fibrin thrombi of the heart, kidneys, and other organs, in four cases. In addition, histologic preparations from 20 cases of myocardial infarction of varying ages were studied in a search for tissue mast cells.

Results

Patients with Carcinoid Tumor.—The hearts and heart valves from patients with carcinoid tumor that had not spread extensively, i. e., that did not involve the liver or distant organs, did not show gross or histologic changes other than those of the usual degenerative type. These changes will be described with the "control" group.

The cases with carcinoid tumor that had metastasized to include the liver were of interest. In six of these no gross valvular or endocardial lesions had been noted at the time of autopsy; microscopically no endocardial changes in the left or the right side of the heart were found. In the three cases with definite valvular involvement the pulmonic valves were thickened by a pearly-gray tissue covering the valves and the orifices were stenotic. In two cases the tricuspid valve was also thickened, but to a less degree. In none of the cases were aortic or mitral changes noted grossly, although microscopic examination of a grossly

Fig. 1.—Normal mitral valve from a case of carcinoid fibrostenosis involving pulmonic and tricuspid valves. Tissue mast cells in valve cusp. Phloxine-methylene blue; reduced to 47% of mag. × 800.



normal mitral valve in one case of carcinoid fibrostenosis showed an infiltration by tissue mast cells (Fig. 1).

Histologically the thickening of the valve cusps was due to the presence of a peculiar fibrous tissue superimposed upon the relatively intact endocardium. This tissue was noted on both sides of the valve cusps and was characterized by a pale eosinophilic and relatively acellular appearance, particularly in the portions that were outermost from the cusps. It was composed of a homogeneous ground substance in which there were occasional condensations of whorled, more deeply eosinophilic-staining fibrous strands surrounding ovoid spaces, some of which contained a pyknotic mononuclear cell. In the bland areas there were relatively few cells, and only rare small vascular channels. Adjacent to the valve cusps, however, in all three cases, there were focal accumulations of mononuclear cells that were identified as lymphocytes, occasional plasma cells, occasional macrophages, and other medium-sized mononuclear cells of an undetermined type. In the fibrous and cellular tissue immediately adjoining the cusps there were many vascular channels, with vessels present in the contiguous endocardium of the cusps as well. These vascular channels were of varying sizes, some quite large (100 times the diameter of a red blood cell), and had thick muscular walls. Near these vessels, both in the valve cusp and in the superimposed fibrous tissue there were striking numbers of tissue mast cells (Figs. 2 and 3). The valve rings had occasional scattered lymphocytes and ovoid and fusiform mononuclear cells, but in general they were not unusual.

With phloxine-methylene blue stain cellular detail was made out most clearly, and it was by use of this stain that the tissue mast cells were best found. With the elastica stain the fibrous tissue present upon the endocardium was clearly demarcated from the relatively intact valve cusp, and was found to be free of elastic fibrils (Fig. 4). The elastic layers of the endocardium of the affected valve cusps were generally intact, although in areas of cellularity and vascularity they were somewhat distorted and reduplicated. With the reticulin stain a moderate number of fine reticulin fibrils were noted in the endocardial fibrous tissue, present as compact whorled masses about the ovoid spaces previously described.

"Normal" or "Control" Cases.—In the heart valves from persons coming to autopsy with various diseases, and designated as "controls" in this study, no lesions were found that approximated those of carcinoid fibrostenosis. Nonspecific valvular changes, excluding calcification, generally consisted of grossly visible fibrous nodularities of the

Fig. 2.—Pulmonic valve from case of carcinoid fibrostenosis. Valve cusp occupies approximately left half of illustration. Note cellularity and vascularity in adjacent fibrous tissue. The large vascular channel in center of illustration is in fibrous tissue adjoining the cusp. Phloxine-methylene blue; reduced to 47% of mag. × 100.

Fig. 3.—Higher power of an area shown in Figure 2. Note mononuclear cells and two tissue mast cells. Phloxine-methylene blue; reduced to 47% of mag. × 800.

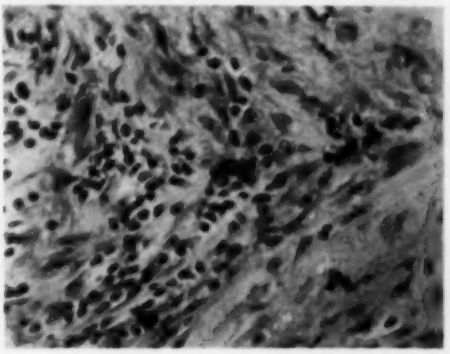


Fig. 4.—Pulmonic valve showing lesion of carcinoid fibrostenosis. Fibrous tissue devoid of elastic fibrils is superimposed upon the valve cusp. Verhoeff's elastica stain; reduced to 46% of mag. × 30.

Fig. 5.—Pulmonic valve from a case of congenital pulmonic stenosis. Cusp is thick and short but supple. Verhoeff's elastica stain; reduced to 46% of mag. × 50.

distal portions of the valve cusps, which on microscopic study were of two types: pale loose fibrillar swellings and dense eosinophilic compact masses. No inflammatory-cell reaction was seen in either type; occasional scattered mononuclear cells and elongated slender cells were commonly found. With the elastica stain these lesions usually contained distorted elastic fibrils. The mitral and aortic valves were more commonly involved by such swellings, the tricuspid valve occasionally, and the pulmonic valve only rarely and to a slight degree.

Congenital Pulmonic Stenosis.—The cases of congenital pulmonic stenosis showed no lesions similar to those of carcinoid fibrostenosis (Fig. 5). Thickened regions of endocardium when present were composed of compact eosinophilic fibrillar strands in which there were few cells. These thickened areas usually, but not invariably, contained elastic fibrils.

Rheumatic Heart Disease.—Early active rheumatic heart disease presented no lesions similar to those of carcinoid fibrostenosis. With the exception of three cases to be noted later, longer-standing cases of rheumatic heart disease with deforming valvular lesions were readily distinguished from carcinoid fibrostenosis. Rheumatic involvement was principally that of the left side of the heart, and when the tricuspid or pulmonic valves were involved, it was almost invariably in combination with mitral or aortic valve involvement.[4] Histologically the lesions differed in that rheumatic valvular deformity was generally the result of scarring of the valve cusp itself, with deposition of densely eosinophilic masses of fibrocollagenous tissue within the cusp. The location within the cusp was confirmed by use of elastica stain, which showed the elastic lamina to enclose the masses of scar tissue, and also to be distorted and separated by the deposition of fibrocollagenous tissue within the endocardium and subendocardium. Elastic fibers generally extended into the masses of dense tissue in a distorted, fanlike pattern. Vascular channels, often present within the substance of the valve cusp

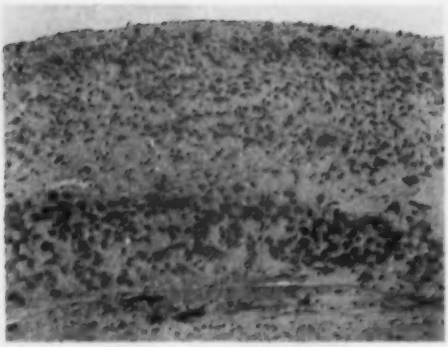


Fig. 6.—Fibrous tissue upon ventricular endocardium in a case of rheumatic heart disease. This resembles the fibrous tissue found in carcinoid fibrostenosis. Hematoxylin and eosin; reduced to 46% of mag. × 200.

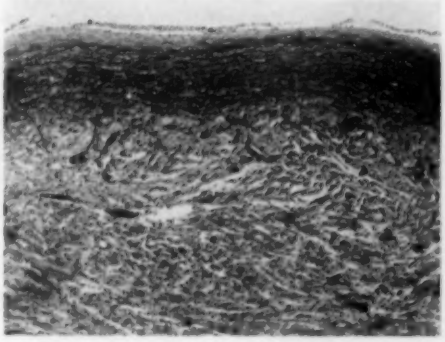
and within the endocardium, were usually of the thick-walled type. In cases of long-standing rheumatic valvular deformity mineral deposition within the valve cusps was common.

In three cases of rheumatic heart disease, two still showing activity as evidenced by the finding of Aschoff bodies, focal endocardial lesions were found that to a degree resembled the changes of carcinoid fibrostenosis. Thickenings were present on the left ventricular and auricular endocardium adjacent to the mitral valve but not involving the valve cusp itself (Fig. 6). The thickened areas did not contain elastic fibrils; they differed from the left auricular thickening commonly found in rheumatic heart disease and designated as a "MacCallum patch."[31] They also differed from the lesions of carcinoid fibrostenosis in the following respects: They were located only on the left side of the heart; they did not involve the valve cusps; a deforming rheumatic intravalvular lesion was present, and Aschoff bodies were found in two of the cases. The endocardial thickening was similar to carcinoid fibrostenosis in certain regions where there was a bland and relatively acellular appearance, with whorled aggregates of fibrous tissue about small ovoid spaces; but this was true only of some areas, so that considerable variation was found in adjacent regions where the bland whorled tissue gave way to dense, compact fibrillar substance, to cellularity, or to calcification.

"Collagen" Diseases.—Cases of so-called collagen diseases did not show lesions that might be confused with those of carcinoid fibrostenosis. The endocardial lesions of lupus erythematosus were of a cellular necrotic verrucous nature, with prominent fibrinoid necrosis. The cardiac lesion of periarteritis nodosa was one of involvement of the coronary arteries, with areas of myocardial necrosis and scarring. The endocardium in the cases studied was relatively normal. In one case of dermatomyositis there were focal areas of myocardium where the muscle fibers were degenerating or had become scarred, without an associated acute inflammatory-cell reaction. In scleroderma the cardiac involvement was one of focal myocardial fibrosis; there were increased vascular channels in the interstitial tissue of the myocardium, fragmentation of muscle fibers, and focal areas of fibrocollagenous tissue. A small localized endocardial thickening was present on the left ventricular endocardium in one case, but this was composed of densely compact eosinophilic fibers and contained elastic fibrils.

Bacterial, Rheumatic, and Nonbacterial Thrombotic Endocarditis.—The lesions of bacterial and nonbacterial thrombotic endocarditis have been presented in detail elsewhere.[32] The valve involvement in bacterial

Fig. 7.—Congenital fibroelastosis, showing abundant elastic fibers in thickened endocardium. Verhoeff's elastica stain; reduced to 46% of mag. × 100.



endocarditis was that of a destructive, highly cellular process, with an acute inflammatory-cell response in the early stages, and with characteristic calcification of vegetations in the healing and late stages. Active rheumatic endocarditis was characterized by necrosis of endocardium and the presence of Aschoff bodies in the heart and valves, with a highly cellular valve response. Nonbacterial thrombotic endocarditis showed dense eosinophilic swellings within the valve cusp, with superimposed blood thrombi over such areas, often at the site of a small endocardial defect.

Fibroelastosis and Other Conditions.—The endocardial thickening of endocardial fibroelastosis was easily distinguished with elastica stain because of its elastic tissue component (Fig. 7). In addition, even with ordinary stains, its appearance was different from that of carcinoid fibrostenosis in that the endocardial thickening appeared as compact uniform eosinophilic fibrillar tissue. Cases of thrombotic thrombocytopenic purpura and fibrin thrombi of organs did not show endocardial lesions. Involvement of the heart was by small granular plugs located within arterioles, capillaries, and venules. These appeared most clearly with use of the phloxine-methylene blue stain, where they were found as blue-green granular thrombi.

Tissue Mast Cells.—Tissue mast cells were found in large numbers in the three cases of carcinoid fibrostenosis, as detailed above; for comparison, sections from each of the conditions listed in this study were stained with the phloxine-methylene blue stain, and a search was undertaken for these cells. Four of ten "control" hearts contained mast cells, which were few in number and were located in one of three areas: In loose epicardial fatty-fibrous tissue, in the loose fibrous tissue surrounding the coronary arteries, or in the interstitial tissue in the myocardium. They were not found in the valve cusps. In cases of benign or metastatic carcinoid tumor without fibrostenotic valvular lesions, mast cells were present only as in control hearts; they were not found in three cases of congenital pulmonic stenosis. In rheumatic heart disease mast cells were present in numbers greater than in the control cases in 3 of 14 cases; they were located in the affected valve cusps as well as in the remainder of the heart, and were generally near regions of increased vacularity of the cusps. Their number, although greater than usual, was considerably less than that seen in carcinoid fibrostenosis. In 12 cases of lupus erythematosus mast cells were found in 2 instances, in only slightly increased numbers, and located in areas of myocardial fibrosis and in interstitial tissue. In eight cases of periarteritis mast cells were present in greater than normal numbers in one case, also located in interstitial fibrous tissue of the myocardium. In bacterial and nonbacterial thrombotic endocarditis mast cells were present in slightly increased numbers only in subacute bacterial endocarditis, where they were found in 2 of 14 cases. They were located in valve cusps, as well as in other areas. Again, their number was less than that of carcinoid fibrostenosis. Mast cells were not found in cases of fibroelastosis, dermatomyositis, scleroderma, thrombotic thrombocytopenic purpura, and fibrin thrombi, but the number of cases of each condition studied was small. In 20 cases of myocardial infarction selected to represent acute, healing, and healed stages, mast cells were noted in every case, but they were generally few in number. They were found in areas of interstitial and epicardial fibrous tissue, and their number and location did not appear to be related to the age of the infarction.

Comment

The valvular lesion in the carcinoid syndrome is considered to be an unusual histologic entity, and one that may be differentiated from other valvular conditions. A peculiar fibrous tissue is present upon the valves and endocardium of the right side of the heart, causing thickening, interadherence, and eventually stenosis of the valve

cusps. Emphasis is directed to the observation that the lesion is not an intravalvular one. With use of elastica stains this fibrous tissue is without elastic fibers, and with phloxine-methylene blue or Giemsa stains, large numbers of tissue mast cells are found near regions of vascularity of the endocardium and in the contiguous fibrous tissue. The possible role of tissue mast cells in the formation of connective tissue, in addition to their demonstrated content of histamine, heparin, and 5-hydroxytryptamine (serotonin)[33] has been suggested in the past.[34]

It was found in this study that in cases where carcinoid tumor had not produced extensive metastases an associated valvular lesion was not present. This is in agreement with most prior reports. Another point of interest is that not all widely metastatic carcinoid tumors were associated with valvular disease. Further study of well-documented cases may indicate whether the length of time that serotonin-producing metastases are present is the explanation for this difference, or whether other factors are responsible. It was noted in this series that only carcinoid tumors arising in the small bowel were associated with valvular disease; this was true also of the cases previously reported in the literature; not all metastatic small-bowel carcinoids were associated with valve changes in this series, however. Two observations that may have bearing on this point are the following: Stout[35] confirmed earlier work by Clara[36] and by Erspamer,[37] noting that the argentaffin-staining characteristic of carcinoids did not hold true for tumors arising in the rectum. Recently Barter and Pearse[38] have presented evidence that the argentaffin-staining characteristic of carcinoids is the result of the formation of a conjugated β-carboline derivative formed from a combination of formaldehyde and 5-hydroxytryptamine present in carcinoid tumors. This might indicate that only carcinoid tumors in certain locations are capable of producing serotonin, and only those that are may give rise to the carcinoid syndrome when sufficient serotonin-producing metastases have been formed.

The limited number of cases available for study has not made it possible to formulate a definite concept of the pathogenesis of the valvular lesions. Attention is called to the finding of inflammatory cells in the valve lesions in at least six previously reported cases. In the four cases that we have been able to study, mononuclear cells, presumably indicative of inflammation, and the finding of newly formed vascular channels in the valve lesions raise the possibility that endocardial inflammation is involved in the formation of fibrous tissue upon the endocardium. The localized endocardial thickenings found in some cases of rheumatic heart disease, where the fibrous tissue bears a limited morphologic similarity to that of carcinoid fibrostenosis, could be interpreted as support for such a pathogenesis. The endocardial fibrous tissue might then represent a proliferative response of the endocardium and would not be the result of the deposition of an adventitious substance upon the endocardium.

It should be pointed out that, with the exception of several of the cases cited in this study, most reports in the literature have not included histologic details of the valvular lesions in carcinoid fibrostenosis. It therefore is not possible to determine whether the valves of the left side of the heart may in some instances be markedly involved in the absence of a right-to-left shunt, such as patent foramen ovale, with high right-side pressure due to pulmonic stenosis. It is suggested that when both left- and right-side heart valve involvement is encountered with a carcinoid tumor a careful histologic study should be made in order to determine whether the left-side involvement is due to previous rheumatic inflammation.

Summary

A comparative histologic study of the heart valves in cases of the carcinoid syndrome (carcinoid fibrostenosis) is presented. The lesions are shown to be unlike those

found in the heart in congenital, degenerative, infectious, and collagen diseases.

The lesions of carcinoid fibrostenosis may be differentiated from other conditions by use of phloxine-methylene blue and elastica stains: A peculiar fibrous tissue devoid of elastic fibers is present upon relatively intact endocardium, and large numbers of tissue mast cells are present in the affected valvular endocardium and in contiguous fibrous tissue.

It was found in this study that cases of carcinoid tumor that had not produced extensive metastases were not associated with valvular lesions, and that not all cases with extensive metastases were associated with valvular changes.

Dr. Henry Tesluk, Dr. Robert Horn, and Dr. Joseph Sieracki, of the Henry Ford Hospital, Detroit, provided us with paraffin blocks of the heart valves from a case of the carcinoid syndrome, and Dr. Victor McKusick, of The Johns Hopkins Hospital, Baltimore, allowed one of us (R. A. M.) to review microscopic sections from one of his previously reported cases. Technical assistance was given by Miss Louise Mertz; photographs are by Mr. Leo Goodman.

Mallory Institute of Pathology (18).

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Pathology of Eosinophilic Granuloma of the Lung

MAJOR DAVID AULD (MC), U. S. A. F.

Introduction

This paper will attempt to define the condition known as eosinophilic granuloma of the lung, first described by Farinacci, Jeffrey, and Lackey [21] in 1951.

The disease is reviewed chronologically as it developed in the literature. Three new cases are described in which the pulmonary involvement was the only recognized expression of the disease. From these and other reported cases the clinical aspects are described, and the pathologic process is reported in detail.

Finally, conclusions are drawn concerning the etiology, pathogenesis, treatment, and prognosis.

Review of Literature

In 1940 Otani and Ehrlich [47] and Lichtenstein and Jaffe [28] independently described a destructive lesion of bone consisting of histiocytes and eosinophils. The latter authors named the process "eosinophilic granuloma of bone" and suggested that it may have a viral etiology in view of negative bacterial cultures. Otani and Ehrlich suggested trauma as a cause and pointed out the similarity of one of their cases to Hand-Schüller-Christian disease. All of the patients recovered.

In 1941 Farber [19] reported 10 cases of the bone disease occurring in children from 3 to 10 years of age and demonstrated its benign nature, with healing occurring spontaneously or following curettage or x-irradiation. He described the pathology as a granulomatous process in which eosinophilic infiltration was frequently, but not always, a prominent feature and noted that foci of necrosis without bacterial involvement were common. He stated that eosinophilic granuloma of bone, Hand-Schüller-Christian disease, and Letterer-Siwe disease were all variations of the same process. Wallgren,[58] in 1940, demonstrated conclusively the unity of the last two conditions.

Green and Farber,[24] in 1942, described five cases of eosinophilic granuloma of bone in children from 11 months to 11 years and pointed out the predominance in males and the predilection for the skull, pelvis, ribs, vertebrae, femur, and humerus. The pathology in the early stage was one of bone destruction with infiltration by eosinophils and large phagocytes; as the lesion aged, eosinophils diminished, and the mononuclear cells became vacuolated, formed foam cells, and then were replaced by fibrous connective tissue and later by bone. The similarity to Hand-Schüller-Christian and Letterer-Siwe disease was again emphasized.

In the same year Gross and Jacox [26] presented cases demonstrating the similarities and transitions between the three conditions. Mallory [39] pointed out that Hand-Schüller-Christian disease was not a "storage" disease, like Gaucher's and Nieman-Pick disease, but an inflammatory granulomatous process with cholesterol storage as a secondary, incidental phase in the progression of

Submitted for publication Aug. 7, 1956.

From the Pathology Service, Fitzsimons Army Hospital, Denver.

Present address: 2750th U. S. A. F. Hospital, Wright-Patterson AFB, Dayton, Ohio.

Col. Howard A. Van Auken and Col. Charles J. Farinacci (MC), U. S. Army, and Dr. Richard M. Mulligan gave valuable suggestions and criticisms, and Mr. William R. Hommel, M.A., did the photography.

An abridgment of a thesis submitted to the Faculty of the Graduate School of the University of Colorado in partial fulfillment of the requirements for the degree of Master of Science, Department of Pathology, 1956.

the disease. He agreed with Wallgren that it represented the subacute form of the process known as Letterer-Siwe disease, and that the bony manifestations were related to those of eosinophilic granuloma.

Currens and Popp,[14] in 1943, described a case showing areas of bone destruction in the left hip and right parietal bones accompanied by bilateral extensive fibrosis of the lungs. This case is similar clinically to the reported cases of eosinophilic granuloma, but the skull lesion was reported pathologically as Hand-Schüller-Christian disease. X-irradiation to the chest resulted in slight improvement of the pulmonary lesions.

Pulmonary involvement accompanying a case of eosinophilic granuloma of bone was reported in 1944 by Engelbreth-Holm, Teilum, and Christensen.[18] In reporting this and four other cases the authors outlined the microscopic pathology in the various stages of the disease, namely, the hyperplastic-proliferative phase, the granulomatous phase, the xanthomatous phase, and the fibrotic, or healing, phase. This description of the process has become classical and has been referred to in many papers on the subject. These authors also showed the similarity to Hand-Schüller-Christian disease and pointed out the transitions between the two. Farber,[20] in 1944, again described the clinical and pathological similarities of the three diseases, and Jaffe and Lichtenstein [31] in the same year reversed their original stand and agreed with Farber, Mallory, and the others. They felt that eosinophilic granuloma of bone represented the mildest and most localized expression of the disorder, while Letterer-Siwe disease was the acute, most generalized, and severest form.

Arnold,[4] in 1946, reported a case of eosinophilic granuloma of the clavicle accompanied by a diffuse soft mottling throughout both lung fields. The bone lesion was successfully treated by curettement, and a total of 6000 r to the chest resulted in definite clearing of the lung. Since then a number of papers have described pulmonary involvement (without pathology studies) accompanying eosinophilic granuloma of the bone, both of the "pure" type [9,16,29,33,44,45,59,60] and of the type clinically suggestive of the Hand-Schüller-Christian syndrome,[3,7,30,35,48,49,53] granting that this is an artificial distinction. In fact, as the literature is reviewed, we find that a number of papers [1,15,20,22,26,28,52,55] documented pulmonary involvement in both Letterer-Siwe and Hand-Schüller-Christian disease, and that the condition known as eosinophilic granuloma of the lung is certainly not a newly discovered entity. This concept is thoroughly discussed by Lichtenstein.[37]

Adams and Kraus,[2] in 1950, reported an unusual case of a 71-year-old woman with a generalized skin eruption, dyspnea, a diffuse mottled infiltration in both lung fields, and a peripheral eosinophilia of 12%. Autopsy revealed numerous discrete and coalescent nodules, up to the size of a hen's egg, in the lungs, which showed microscopically granulomas with eosinophilic infiltration, severe blood vessel changes, and necrosis. Similar lesions were found in the kidneys and skin, but not in the liver, spleen, or bones. The disease process was not thought to be related to eosinophilic granuloma of bone, and its similarity to periarteritis nodosa was discussed. Other papers have reported eosinophilic granuloma in the skin,[36] vulva,[42] and gastrointestinal tract.[57]

Farinacci's paper,[21] in 1951, described two cases in which lung biopsy revealed an eosinophilic granulomatous lesion resembling eosinophilic granuloma of bone. The first of these was a 32-year-old man with a productive cough, weight loss, and bilateral pulmonary infiltrate. The second was a 24-year-old man whose routine chest x-ray showed a diffuse type of increased density throughout both lungs. There was a history of cough and sputum production for several years; the leukocyte count was 14,250, with 60% neutrophils and 10% eosinophils. No extrapulmonary lesions were found in either case. Histologic study revealed fibrosing granulomatous lesions infiltrated with eosinophils. The histiocytes had large vesic-

ular nuclei; the cytoplasm of some was fragmented; in others it was abundant and vacuolated. Cultures of the material were negative for Mycobacterium tuberculosis and fungi, and no organisms were demonstrated in the lesions. The authors concluded that the lesions "are, like eosinophilic granuloma of bone, the monosymptomatic form of a systemic xanthomatous disorder."

May, Garfinkle, and Dugan,[40] in 1954, reported three cases of eosinophilic granuloma of the lung with pathology studies; two of these were associated with similar osseous lesions proved by biopsy, and one had the Hand-Schüller-Christian syndrome and a femoral bone lesion. The pulmonary lesions in all three cases were essentially similar histologically; they consisted of nodular areas of histiocytes infiltrated with varying numbers of eosinophils and smaller amounts of lymphocytes and neutrophils. The histiocytes had a moderate amount of foamy or pale granular cytoplasm, and in two of the cases xanthomatous histiocytes were numerous. The stroma in some areas was scant; in others increasing amounts of collagenous tissue were found. Occasional giant cells were seen. Subintimal proliferation in the arterioles and venules was mentioned in one case but was considered nonspecific. Infiltration of alveolar walls with histiocytes, eosinophils, lymphocytes, and plasma cells was noted, and all the cases had some degree of emphysema. In discussing the natural history of the lesion, the authors stated that in the smaller nodules the infiltration was of an interstitial nature; with growth, eosinophils became numerous, and the alveolar walls thickened and obliterated the air spaces. These foci coalesced and formed the larger nodular lesion replacing the lung parenchyma, although the interstitial reaction persisted at the periphery. The emphysema was thought to antedate the granulomatous lesions.

Mazzitello [41] reported two more cases of pulmonary eosinophilic granuloma without other demonstrable lesions. In the first case a diffuse nodular disease was found throughout the lung, the nodules measuring 4-10 mm. These were made up of moderately large cells with oval nuclei that had a fine chromatin pattern, and a number of eosinophils were sprinkled throughout the mass. Lymphocytes and macrophages surrounded the lesions, and the adjacent alveolar septa were thickened with lymphocytes and macrophages. No organisms or foreign bodies were found. Some of the arteries in the area showed hyaline thickening and inflammation, but the author did not comment on this finding. In the second case a diffuse nodularity was again found, the lesions measuring up to 1.5 cm. in diameter. Microscopically they were composed of reticulum cells and foam cells, with some lymphocytes at the periphery. Eosinophils were scattered through the lesions but were most abundant at the center. No mention was made of emphysema in either case. Both cases were treated with corticotropin and became asymptomatic. A follow-up chest x-ray in Case 1 showed bilateral clearing.

Childers, Middleton, and Schneider,[11] in 1955, reported a case of eosinophilic granuloma of the femur and lungs in a 24-year-old white man. At thoracotomy dense adhesions were found over most of the upper half of the right upper lobe. Under the pleural surface of the lobe were discrete, hard, grayish-yellow nodules 2-10 mm. in diameter. Microscopic sections showed subpleural and interstitial focal collections of eosinophils and large mononuclear cells. The centers were predominantly histiocytes, and the eosinophils were most marked at the periphery. Occasional multinucleated histiocytes contained a few small vacuoles, but fat stains were negative. The femoral lesion was discovered after the lung biopsy and had a histologic pattern similar to the pulmonary nodules. The patient was treated with x-rays to the chest and femur; follow-up chest films showed progressive resolution of the process, and the bone lesion healed rapidly.

Grant and Ginsburg,[23] in 1955, presented a case of a 32-year-old man with eosino-

philic granuloma of the lung and diabetes insipidus. At operation the pleura was found to be intact, but numerous nodules were palpable in all lobes. The pathologist reported cystic spaces closely related to bronchioles, lined with granulomatous tissue, and heavily and diffusely infiltrated by eosinophils. There was no necrosis, giant-cell formation, or foam cells. The patient was treated for a month with corticotropin and was discharged much improved. The diabetes insipidus was controlled with posterior pituitary U. S. P. (Pituitrin) snuff.

The most recent report is that of Virshup and Goldman,[56] in 1956, which describes another case of solitary involvement of the lung in a 15-year-old white youth. Exploration of the chest showed small air-containing cysts, measuring up to 1 cm., over the surface of the lung and shotty nodules, 3-7 mm., scattered diffusely throughout the parenchyma. Microscopically there were aggregates of large fusiform or stellate histiocytes with vesicular nuclei intermixed with abundant eosinophils. Several of these nodular areas showed varying amounts of fibrosis, and in places there was extensive fibrous replacement of the lung architecture. In other areas were found emphysema or cyst-like spaces lined by fibrous or granulomatous tissue with occasional bronchiolar communication. The patient was treated with antibiotics, and nine months postoperatively some clearing was evident in the chest x-ray.

Report of Cases

Case 1.—A 20-year-old white male soldier was transferred to this hospital on May 13, 1952, with a diagnosis of pulmonary sarcoid. He had noticed pain in the right hemithorax on raising the arm six months previously, and an x-ray taken at the time was suggestive of tuberculosis. At another hospital smears and cultures were negative for M. tuberculosis, and tuberculin skin tests repeated several times were negative. Two months before transfer he complained of slight dyspnea, and during this period complained of a moderate dry cough, but no sputum production, fever, severe dyspnea, or pneumothorax. The highest sedimentation rate reported was 12 mm/hr.

The past history revealed that the patient broke a barrelful of fluorescent light tubes in 1948 but was otherwise negative. Physical examination on admission revealed no abnormalities.

A chest x-ray (Fig. 1) showed "a nodular type of infiltration involving the entirety of both lung fields, more marked in the apical areas. There is no mediastinal adenopathy, and the size and contour of the heart are normal." The film

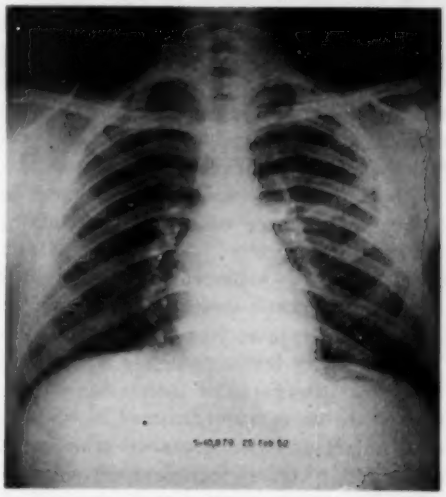


Fig. 1 (Case 1).—Chest x-ray, showing fine nodular infiltrations in both lung fields.

was interpreted as representing Boeck's sarcoid or pulmonary tuberculosis. A long-bone survey was negative. Leukocyte count 13,800, with a normal differential; eosinophils 3%. The remainder of the hemogram was normal, as was the urinalysis. Total serum proteins were 5.7 gm. per 100 cc., with albumin 2.4 gm. and globulin 3.3 gm. A repeat showed 6.8 gm. per 100 cc., with albumin 3.3 gm. and globulin 3.5 gm. A serologic test for syphilis was negative. Skin tests for tuberculosis, coccidiodomycosis, and histoplasmosis were negative, and sputum and gastric smears and cultures were negative for M. tuberculosis and fungi.

Biopsies of lymph nodes from the right axilla and the left cervical region were done on May 20 and June 5, respectively, and were reported as showing reactive hyperplasia without evidence of any granulomatous lesions. On Aug. 14, 1952, a left exploratory thoracotomy was performed through the sixth interspace. Examination of the right hemithorax disclosed no enlarged lymph nodes. The pleura was normal, but fine nodularities could be palpated throughout the lung. A wedged biopsy specimen was taken from the right lower lobe, and the pathologic diagnosis was

eosinophilic granuloma. Smears and cultures of the material were negative for pathogenic bacteria, M. tuberculosis, and fungi. The patient made an uneventful recovery. No specific therapy was given. The patient was discharged from the hospital asymptomatic on Oct. 9, 1952, although a final chest x-ray showed no change during his hospital stay. Correspondence with the patient in March, 1954, or 28 months after the onset of symptoms and 19 months after operation, disclosed that he was still asymptomatic and doing a full day's work.

CASE 2.—A 23-year-old white male soldier was transferred to this hospital from Japan on Oct. 15, 1954, because of a diffuse pulmonary infiltration and spontaneous right pneumothorax.

The past history was not significant. In December, 1952, he developed a cough which lasted eight weeks. In July, 1953, he experienced a sudden sharp pain in the left hemithorax while lifting a heavy object and remained short of breath for several days. In January, 1954, he was given penicillin because of fever and malaise, after which he noted a persistent cough, productive of a small amount of sputum in the early morning. In June, August, and September of 1954 he again noted sharp pain and dyspnea; chest x-rays during the last two attacks showed a diffuse pulmonary fibrosis involving all the lobes and right pneumothorax. A closed-tube drainage was performed before transfer to this hospital, and the lung reexpanded satisfactorily.

Admission physical examination was negative except for a few small lymph nodes in the neck, axillary, and inguinal regions. He was slightly short of breath on exertion and complained of minimal thoracic pain on deep breathing. Chest x-rays showed a diffuse pulmonary infiltrate with emphysematous changes. A review of his preinduction film, of January, 1952, showed small patchy nodular densities scattered throughout the pulmonary areas bilaterally without evidence of cavitation (Fig. 2).

The hemogram, urinalysis, and cardiolipin microflocculation test were normal on admission, but most of the successive leukocyte counts varied between 12,000 and 17,000, with 0-8% eosinophils. The average erythrocyte sedimentation rate was 24 mm/hr. Total serum proteins were 7.9 gm. per 100 cc., with albumin 4.2 gm. and globulin 3.7 gm. The serum calcium was 10.4 mg. per 100 cc. Stool examinations for ova and parasites were negative. L. E. cell preparations on peripheral blood were negative, and a bone marrow study was normal. Skin tests were negative for tuberculosis, coccidiodomycosis, histoplasmosis, and blastomycosis, and serologic tests for the three fungous diseases were negative. Smears and cultures of sputum and gastric washings were negative for M. tuberculosis and fungi. X-rays of the hands, feet, and ankles and an upper gastrointestinal series were negative.

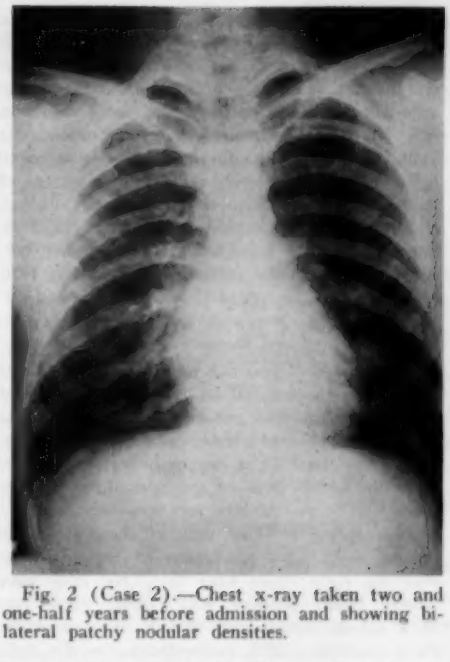


Fig. 2 (Case 2).—Chest x-ray taken two and one-half years before admission and showing bilateral patchy nodular densities.

On Nov. 5, 1954, biopsy of a subclavian fat pad and lymph node showed moderate chronic inflammation and reticulum-cell hyperplasia. Five days later spontaneous left pneumothorax was treated successfully by closed-tube drainage. On Nov. 15, a left thoracotomy was performed. The lower lobe was collapsed. A few adhesions were found between the upper lobe and the chest wall laterally and at the apex. Subpleural cystic areas were found over the entire lung and measured 5-10 mm. except at the apex, where several were as large as 3 cm. Palpation of the lung revealed firm granular areas throughout all of the parenchyma. No lymph nodes were palpable in the mediastinum. A wedge biopsy specimen was taken from the free edge of the lingula. The pathologic report was "eosinophilic granuloma with cystification." Cultures were negative for pathogenic bacteria and fungi, and smears and cultures were negative for M. tuberculosis. The postoperative course was stormy, and pneumothorax occurred bilaterally, requiring thoracotomies and thoracoplasty. The last pneumothorax was in March, 1955.

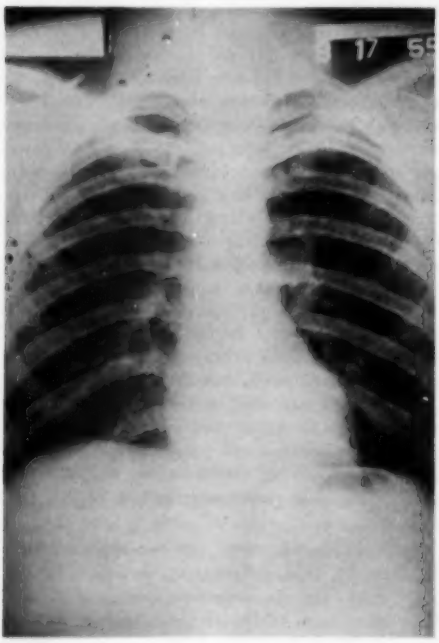
Corticotropin was given for two months, starting Nov. 19, 1954, followed by cortisone, 50 mg. twice daily for six months. During this time there was some subjective improvement, but no

significant change was noted in the chest x-rays. The patient was discharged on May 31, 1955, and was followed in the outpatient clinic. Several months after the start of steroid therapy an acne-like rash developed on the face, shoulders, and back, which improved on treatment. In July, 1955, several indurated, well-circumscribed lesions developed in each axilla. Biopsy of one of these led to the diagnosis of eczyma, although a dermal infiltrate containing histiocytes and inflammatory cells was described. The last correspondence with the patient was in March, 1956, at which time he stated that his cough and expectoration had decreased, and that he was generally improved and working eight hours a day.

CASE 3.—A 24-year-old white male soldier was referred to the hospital on July 14, 1955, because of right spontaneous pneumothorax and a diffuse bilateral pulmonary nodular infiltration. The patient complained of a nonproductive cough and a 10 lb. weight loss in the past three to four months. The past history was noncontributory.

Examination revealed reduced chest expansion on the right with diminution of breath sounds over the right upper lung field. No rales were heard. Blood pressure was 118/65, pulse rate 76 a minute, temperature 98.4 F. X-rays of the chest revealed a 20% pneumothorax on the right and nodular streaked infiltrative densities in both lung fields. A bone survey, including the skull, was normal. Hemoglobin was 16.4 gm. per 100 cc.; hematocrit 50; sedimentation rate 28 mm/hr. Leukocyte count 12,000, with a differential count of 70% neutrophils, 25% lymphocytes, 3% monocytes, and 2% eosinophils. The urinalysis and cardiolipin microflocculation tests were negative. Total serum proteins were 7.3 gm. per 100 cc., with albumin 3.3 gm. and globulin 4.0 gm. A repeat test reported albumin 3.9 gm. and globulin 3.4 gm. per 100 cc. Blood cholesterol was 161 mg. per 100 cc., with esters 77%. Thymol turbidity was 3 units; the cephalin flocculation test was negative. Prothrombin time was 70%. Two sputum smears were negative for acid-fast bacilli. Skin tests were negative for tuberculosis, coccidiodomycosis, and histoplasmosis.

Fig. 3 (Case 3).—Chest x-ray, bilateral patchy infiltration.



On Aug. 1 a scalene lymph node biopsy was reported as normal. An exploratory thoracotomy was performed on Aug. 19 through the right fourth interspace. Many fine adhesions were found between the upper lobe and the apex of the chest cavity, as well as the mediastinum. Several lymph nodes were palpable, and a soft, succulent node, 1.0×1.5 cm., was dissected from the posterior surface of the common basal bronchus. One very small bleb was found on the surface of the apical segment anteriorly, and multiple nodules, 1-4 mm. in diameter, were palpated, mainly in the upper lobe, the hilar portion of the middle lobe, and the superior segment of the lower lobe. When they occurred near the pleural surface, they appeared pale gray and oval. A biospy specimen was taken from the superior segment of the lower lobe and was reported as eosinophilic granuloma. The lymph node was said to show reticulum-cell hyperplasia.

The postoperative course was uneventful. On Sept. 10, radiation therapy was instituted with 600 r, in air, to each anterior and posterior thoracic region. The patient was asymptomatic when discharged, on Oct. 31, and a final x-ray showed some clearing in the lower two-thirds of each lung field. Correspondence with the patient on Feb. 28, 1956, indicates that he has a mild nonproductive cough and notices tightness in the chest in cold weather, but is doing a full day's work.

Clinical Studies

Thirteen cases of eosinophilic granuloma of the lung proved by biopsy have been reported. In eight of these, including the three reported in this paper, the pulmonary changes were the only known manifestations of the disease.[21,41,58] Four were accompanied by bone lesions,[11,40] and one had diabetes insipidus.[23] The clinical manifestations

of the pulmonary lesions were similar in all cases regardless of the presence or absence of extrapulmonary involvement.

As with eosinophilic granuloma of the bone, males are affected oftener than females, in this series in a ratio of 11:2. The age group is somewhat older, the ages ranging from 15 to 40, with most cases in the early 20's. The race was not stated in four cases, but all the rest were Caucasians.

The symptoms are mild, and the onset of the disease is insidious. The duration is usually several months to a year, although many patients can recall vague complaints for several years. In a few cases in which old x-rays were reviewed minimal, but definite, changes were found while the patient was entirely asymptomatic. Cough, with or without sputum production, is found, and moderate dyspnea and chest pain are noted in many instances. Weight loss of 10-15 lb. is not uncommon. Pneumothorax was a prominent feature of four cases. Chills, fever, and night sweats are rarely seen. Most patients complain of some degree of malaise and fatigability.

Physical examination usually reveals nothing of note except in the case of pneumothorax. Otherwise the patient appears healthy, but a few rales are occasionally heard. There is no significant lymphadenopathy in any case. Most unusual is the afebrile course of the disease.

A few laboratory findings are significant. The leukocyte count is usually over 10,000 per cubic millimeter. The differential count shows a preponderance of neutrophils, and a mild eosinophilia (3%-10%) is found in about half the cases. The sedimentation rate is almost always elevated. Urinalysis, serology, and blood chemistry are not remarkable, except that an albumin-globulin reversal is occasionally noted. Cultures of sputum for bacteria and fungi are consistently negative.

The chest x-ray shows a diffuse bilateral linear or nodular infiltrate. Cystic areas within the lung itself or blebs on the pleura may be found.

The treatment of these cases was largely experimental, and all the patients improved symptomatically with or without therapy. Three of the thirteen received no treatment, and the x-ray remained unchanged. Five were treated with steroids; "moderate" x-ray clearing was noted in three. Three were treated with x-radiation; one showed marked clearing; one, moderate clearing, and one, no change. One case was given massive doses of antibiotics, without x-ray improvement, and another patient received a course of neoarsphenamine, with no x-ray clearing.

Follow-ups are reported up to three and one-half years. All of the cases reported to date became stabilized, and most of them remained asymptomatic.

Pathologic Anatomy

The microscopic pathology of the three cases reported above is essentially the same, and all will be reported together, reference being made to the individual case when differences occur. In addition, Dr. Farinacci has made available the material from his cases,[21] which were also reported from this hospital, and these will be referred to as Cases F1 and F2. Slides from all the cases were stained with hematoxylin and eosin; in addition, the material from Cases 2, 3, and F2 was stained with Masson's trichrome stain and with Wilder's reticulum, Verhoeff's elastic tissue, and MacManus' periodic acid-Schiff stains. The gross descriptions are taken from our cases and those of Farinacci, as well as from the operative reports found in the papers of Mazzitello,[41] May,[40] Childers,[11] Virshup,[56] and Grant.[23] These represent a total of 13 cases.

Gross Pathology.—The visceral pleura may or may not be involved. In five of the above cases adhesions were mentioned, and in most of these they were fine and not extensive. In only one case were they described as dense. Blebs or cysts on the surface of the lung are described in four patients; two of these had one cyst each, both apparently small, and the other two

showed many cysts on the lung surface, from 0.5 to 3 cm. in diameter. All four of these patients had episodes of pneumothorax, but this symptom was lacking in the patients without blebs. No pleural effusion was mentioned in any of the cases.

The lesions within the lung tend to be small, being described in most instances as granular, but in some as large as 1.5 cm. They are diffusely scattered throughout the lung, with a tendency to become confluent at the hilus but without any special relation to the bronchi. When they appear subpleurally, they have a dark-gray color, and the overlying pleura may be puckered or dome-shaped. The nodules are firm, but never stony-hard, and when cut appear grayish-white or tan. The margins are indistinct and do not have the appearance of encapsulation (Fig. 4). Caseation is not seen.

Enlarged hilar lymph nodes are not common, although an occasional soft node as large as 1.5 cm. may be found.

Microscopic Pathology. — The essential cellular components of the lesion are histiocytes and eosinophils (Fig. 16). The former are moderately large pale cells with centrally placed round to oval, pale-staining vesicular nuclei. The nuclear chromatin is finely divided, and a single nucleolus is prominent. Cell outlines are fairly well defined in many sections, but in the denser areas the cells blend into a sort of syncytium. The cytoplasm is granular, light pink when stained with hematoxylin and eosin, and reddish-brown with Masson's trichrome stain. Occasional cells are vacuolated, but no true foam cells were found in our material similar to those illustrated by May.[40] A few multinucleated forms are seen, and these presumably result from fusion of several histiocytes. As many as 20 nuclei may be found scattered all through the cell. Most of the eosinophils are bilobed, but immature forms are also seen.

The lesions are in the form of granulomas in the interstitial tissue. Typically there are confluent masses of histiocytes sprinkled with varying numbers of eosinophils (Figs. 4, 5). There is an arteriolitis, and eosinophils may be found in the intima, media, and adventitia (Figs. 12, 13). Fibrinoid degeneration is seen, particularly in the adventitia, and the cells of the intima appear swollen and tend to obliterate the lumen. The fibrinoid material stains bluish-purple with the periodic acid-Schiff reagent, and similar material may be found in amorphous clumps and strands throughout the lesion. An interstitial inflammation is found in the surrounding parenchyma in some instances, and the alveolar septa are infiltrated with eosinophils, lymphocytes, monocytes, and plasma cells (Fig. 8). Necrosis is observed in the center of some of the larger lesions, and bronchial communications can be demonstrated (Figs. 6, 7). Fibrosis, with or without eosinophilia, may also be seen (Fig. 9). Emphysema is common in areas of the lung not directly involved with the inflammation, and cysts lined by histiocytes may be found in many sections (Figs. 10, 11).

Fig. 4 (Case 1).—Biopsy specimen. Hematoxylin and eosin; 48 mm. Micro Tessar.

Fig. 5 (Case 1).—Granulomatous mass showing distribution of histiocytes and eosinophils. Hematoxylin and eosin; reduced to 60% of mag. × 90.

The pleura may be secondarily involved, and may be edematous, inflamed, fibrotic, or cystic, depending on the behavior of the underlying lesions.

Hilar lymph nodes were studied from Cases 3 and F1. In each case the nodes were enlarged, and many pink histiocytes were found in a random distribution between the lymphoid follicles. In both cases the nodes contained large numbers of eosinophils, but no granulomas or arteritis was found. Scalene node biopsy was done in Case 3; this again showed numerous pink histiocytes, but eosinophils were scarce. Right axillary and posterior cervical lymph nodes from Case 1 and a right epitrochlear node from Case F1 showed similar histiocytes without eosinophils. Tonsillectomy was done on Case F2, and the specimen showed only chronic tonsillitis.

Smears of sputum and bronchial washings were made in Case F1 and showed interesting results. Mucopurulent material was found in each specimen, along with large numbers of eosinophils. These were especially numerous and well preserved in the bronchial washings (Fig. 18) and suggest these studies may be of diagnostic value.

None of the stigmata of bronchial asthma were found in our five cases.

Comment

The histopathology outlined above is, of course, limited in its scope in that the material was taken from only five cases. All biopsy specimens were from peripheral areas of the lung, and mediastinal lymph nodes were submitted in only two cases. Much more information must be obtained from a study of the lungs as a whole, with particular reference to the larger blood vessels and bronchi. One case report[40] describes a right upper lobe, resected on a frozen-section diagnosis of cancer, which contained six eosinophilic granulomatous lesions in the parenchyma, not associated with bronchi. The large vessels and bronchi were not described.

Fig. 6 (Case 2).—Bronchial communication with granulomatous mass partially fibrosed. Hematoxylin and eosin; reduced to 60% of mag. × 45.

Pathogenesis.—The lesion seems to begin in the interstitial tissue as a focal granuloma; some are intimately related to arterioles (Figs. 12-14), while others are independent of the blood vessels. In this stage eosinophils are found in the intima, media, and adventitia. There is a proliferative endarteritis, and the endothelial cells become swollen and narrow the lumen. Surrounding the artery are a number of eosinophils, lymphocytes, plasma cells, and monocytes scattered among the histiocytes, and in some sections a thick acidophilic mantle is formed in the adventitia. The changes resemble those of periarteritis nodosa in its early stages. A rare venule may show a similar inflammation, and eosinophils may appear about irregular masses of bright pink acellular material (Fig. 15). The alveolar structure is preserved in the younger lesion, indicating a degree of reversibility.

With progression of the process the histiocytes advance in a wave over the pulmonary tissue: Bronchioles, alveolar ducts, and alveolar septa are infiltrated and destroyed. The resulting picture is a uniform sheet of histiocytes sprinkled with eosinophils (Figs. 5, 13). The pulmonary tissue surrounding the mass meanwhile undergoes an interstitial inflammatory reaction. The septa are infiltrated with histiocytes, eosinophils, and monocytes, and large numbers of macrophages are found in the alveoli (Fig. 8). An obstructive emphysema develops (Fig. 10), due to infiltration of the bronchiolar wall (Fig. 17). Rupture of emphysematous blebs probably accounts for the pneumothorax observed in three patients.

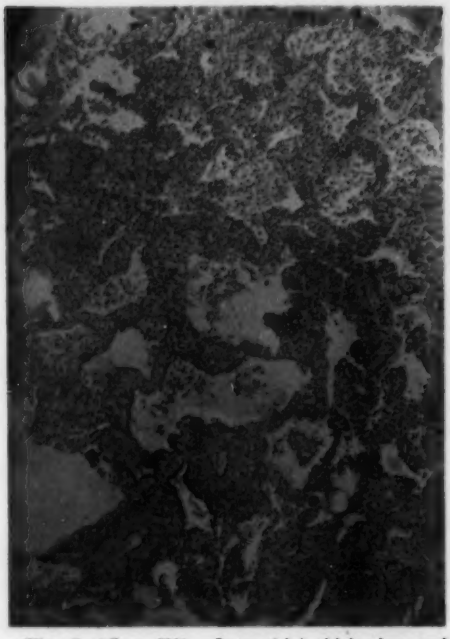
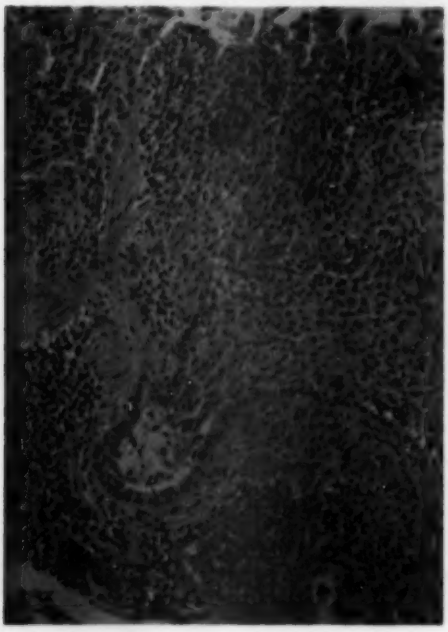


Fig. 8 (Case F2).—Interstitial thickening and inflammation. Hematoxylin and eosin; reduced to 60% of mag. × 90.

Fig. 7 (Case 1).—Masses of histiocytes and eosinophils emptying into bronchiole. Hematoxylin and eosin; reduced to 60% of mag. × 225.



As the arteriolitis obliterates the vessel lumen, the blood supply of the lesion is diminished, and necrosis occurs. The weakened bronchiolar walls may rupture, allowing the softened granulomatous mass to pour into the bronchial tree (Fig. 7). A communicating cavity may form (Fig. 6); this may persist, expand into a large bleb (Fig. 11), and later rupture into the pleural space. Or the communication may

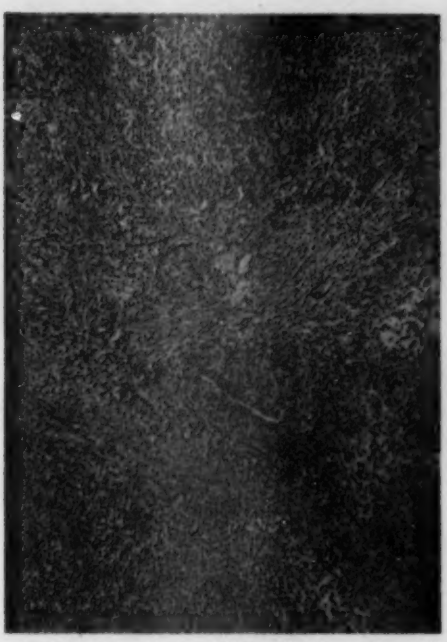


Fig. 9 (Case F2).—Older, fibrotic nodule still heavily infiltrated with eosinophils. Hematoxylin and eosin; reduced to 60% of mag. × 75.

close, as is probably more frequently the case, resulting in resorption of the trapped air and collapse, with eventual formation of a fibrous scar. Fibroblastic proliferation also accompanies the enlargement of the lesion, and fibrous tissue may replace all or part of the granuloma, preventing cystification of that particular mass. In this instance one finds a hard, fibrotic nodule composed of fibroblasts and collagen fibers with varying numbers of eosinophils (Fig. 9). Combinations of the cystic and fibrotic phases may be found. Thus one may observe a cyst communicating with a bronchiole; lining the cyst may be histiocytes, and peripheral to this may be a zone of dense fibrous tissue, all with or without eosinophilia (Fig. 6).

The eosinophil may be found in both the early and the late stage and is not an indication of age. When it is present, there is a surrounding zone of inflammatory reaction; when it is no longer found, the adjacent tissues appear relatively normal. Discrete masses of histiocytes with various degrees of cyst formation may be found in the pulmonary parenchyma during the quiescent period (Fig. 10), or a typical scar may form, free of eosinophils. Hence the interpretation of a lesion must take into account its stage of development—early or late—and its eosinophil content, indicating its activity.

The study in this paper indicates a widespread recurrent process of destruction and repair. The granulomatous phase begins apparently as a response to some unknown irritant. The lesion at first compresses and infiltrates adjacent structures, and as growth continues destroys them and becomes necrotic, with arteriolar obliteration. This is followed by cyst formation and fibrosis. Lesions in all stages may be found in one small specimen, indicating that new ones are forming and reacting, while the older ones are healing or still smoldering under the influence of the offending agent. Many lesions probably

Fig. 10 (Case 3).—Quiescent mass of histiocytes with absence of surrounding inflammation. Note emphysema. Hematoxylin and eosin; reduced to 60% of mag. × 45.

regress and heal during the early stages; else the patient would succumb in a short time, considering the great activity and widespread distribution of the process. One is surprised by any regression at all in the x-rays following treatment, considering the amount of destruction found on the microscopic slides. Permanent fibrosis of some degree does occur, as demonstrated by x-ray, but cystic changes enough to cause symptoms were found in only four of the reported cases. One wonders whether many of the old cases of pulmonary fibrosis of unknown etiology begin with this process.

Etiology.—Several theories of etiology have been advanced, but none have been proved and most can be ruled out by the clinical and pathologic findings. The following conditions might be considered in relation to eosinophilic granuloma:

1. Bacterial or Mycotic Infection: Repeated cultures have always been negative for bacteria and fungi. The mild clinical course and the absence of fever tend to discount an infection, although a leukocytosis usually exists. Regional lymph nodes do not show the reactive hyperplasia typically found in infectious processes.

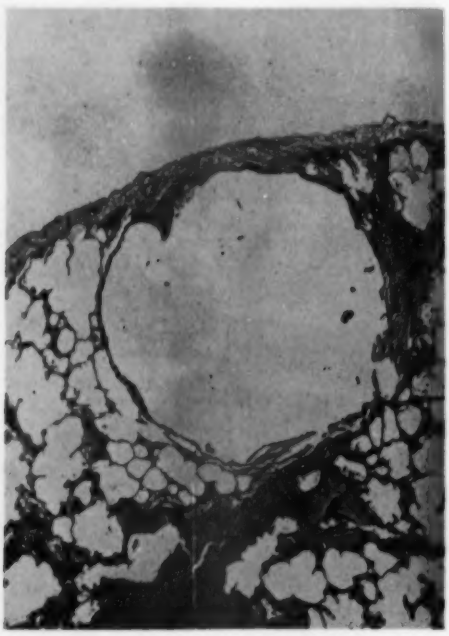


Fig. 11 (Case 3).—Bleb lined by histiocytes. Hematoxylin and eosin; reduced to 60% of mag. × 40.

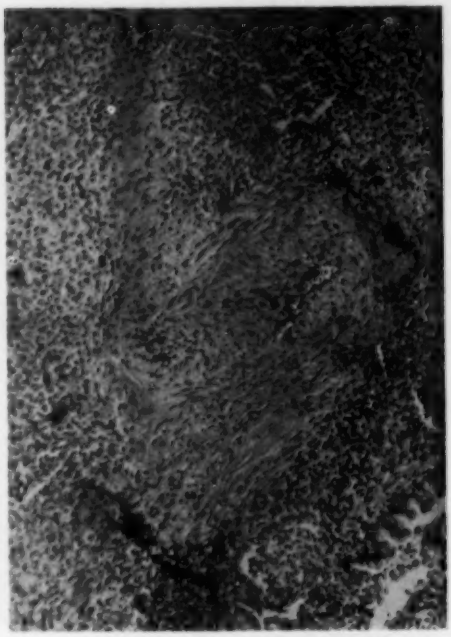


Fig. 12 (Case 3).—Acute arteritis with eosinophilic infiltration. Hematoxylin and eosin; reduced to 60% of mag. × 200.

2. Viral Infection: Viral studies have not been reported in eosinophilic granuloma, but the granulomatous inflammation bears no resemblance to known viral diseases. No inclusion bodies were found in the material studied; hyperplasia of epithelium does not occur. Lymphocytosis has not been found in the peripheral blood. Transmission of the disease has never been reported.

3. Helminthic Infestation: Tissue and peripheral eosinophilia are well known in this group of diseases, and a granulomatous type of inflammation is common. However, in none of the reported cases were parasites found in the tissues. Stools were examined in many instances and were negative for ova and parasites. None of the patients complained of gastrointestinal disturbances.

4. Hodgkin's Disease: Reticuloendothelial proliferation, giant-cell formation, fibrosis,

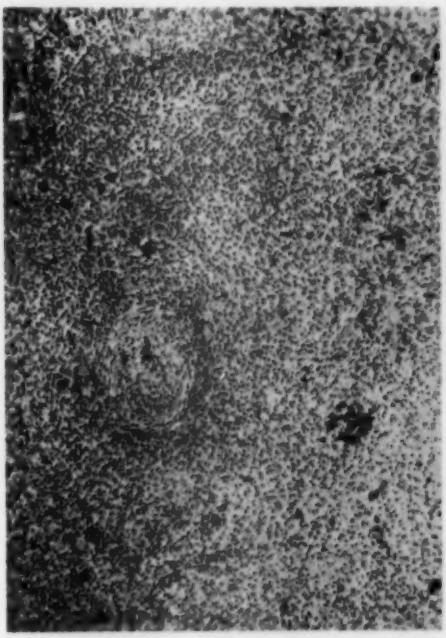


Fig. 13 (Case 1).—Inflamed blood vessel within a granulomatous vessel. Hematoxylin and eosin; reduced to 60% of mag. × 175.

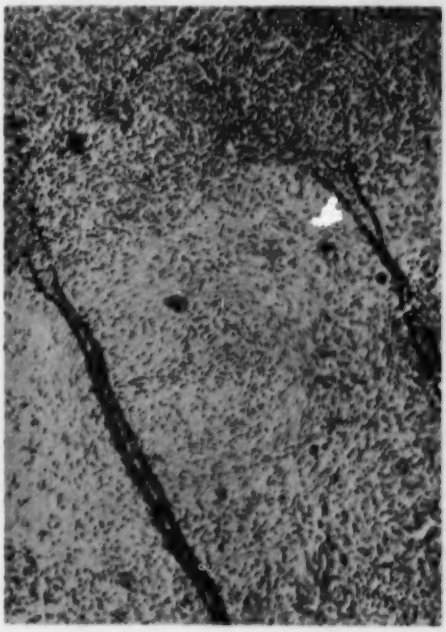
necrosis, and sometimes eosinophilia characterize this condition. Although Hodgkin's disease may involve the lung, the disease primarily affects lymphoid tissue; the eosinophilia is usually not intense, and the Reed-Sternberg cell bears no resemblance to the giant cell of eosinophilic granuloma. The general benignancy of the latter condition does not favor its being a variant of Hodgkin's disease.

5. Berylliosis and Sarcoidosis: These disorders have similar microscopic patterns and may involve the lung in a diffuse granulomatous process. Caseation is not found, and fibrous replacement of the lesion is a common sequel. The histiocytes and giant cells appear identical with those of eosinophilic granuloma, but tissue eosinophilia is minimal. Most of the lesions are discrete and sharply outlined, and the surrounding lung tissue is usually uninvolved, in contrast to the active lesions in eosinophilic granuloma and the adjacent interstitial inflammation. Beryllium inhalation may have occurred in one of the cases reported above following breakage of fluorescent light bulbs, but this is the only such exposure recorded in this disease.

6. Hypersensitivity: None of the authors writing on the subject of eosinophilic granuloma of the bone or lung has considered the possibility that the condition may represent a hypersensitive state. The presence of the eosinophils has apparently been ignored in speculating on the etiology, despite the fact that an inflammatory response of this nature is quite remarkable. The eosinophil is found in all parts of the granulomatous nodule, from the center to the periphery, as well as in the surrounding alveolar septa. A tissue eosinophilia is almost always an indication of hypersensitivity and is seldom seen otherwise, particularly in the large numbers described in our cases.

The peculiar arteriolar reaction has almost gone unnoticed, and no significance was given it by the writers who described

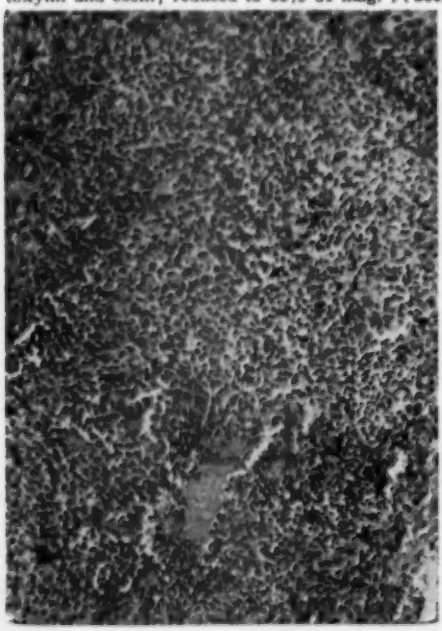
Fig. 14 (Case 3).—Necrotizing arteriolitis, late fibrotic stage. Hematoxylin and eosin; reduced to 60% of mag. × 175.



it. Eosinophils, as well as plasma cells, lymphocytes, and neutrophils, may be found in all three layers of the artery. Fibrinoid degeneration is found in the adventitia, and there is a proliferation of endothelial cells. These findings, along with the eosinophilia, strongly suggest a hypersensitivity reaction, and I feel that the condition is basically an allergic angiitis related in some way to periarteritis nodosa.

Relation to Known Hypersensitive States.—Lewis and Cormia [36] reported a case of eosinophilic granuloma of the skin associated with marked skin hypersensitivity. Treatment of a Trichophyton infection of the feet resulted in exacerbation of the eosinophilic granuloma, and new granulomas appeared at the sites of trichophytin injections. The authors demonstrated the histologic similarity to periarteritis nodosa and felt that the initial change was in the blood vessels. The case of Adams and Kraus [2] supports this view by showing eosinophilic granulomatous lesions in the skin, lungs, and kidneys associated with a panarteritis.

Fig. 15 (Case 3).—Pink acellular material in the center of an inflammatory reaction. Hematoxylin and eosin; reduced to 60% of mag. × 200.



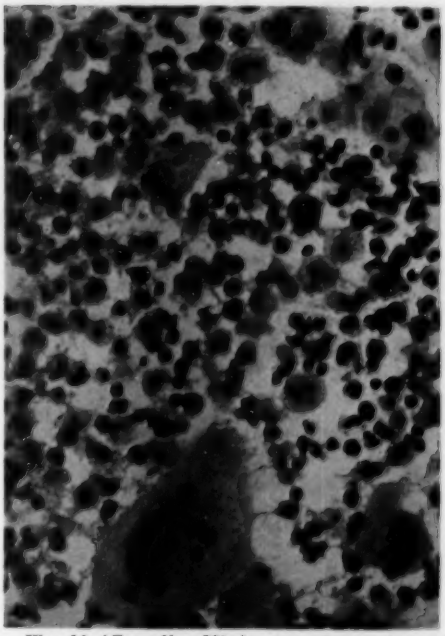


Fig. 16 (Case 3).—Histiocytes, giant cells, and eosinophils. Hematoxylin and eosin; reduced to 60% of mag. × 875.

Sweeney and Baggenstoss [54] described granulomatous lesions in their cases of periarteritis nodosa involving the lungs. Some of the parenchymal lesions were closely associated with arterial lesions, while others were seemingly independent of the vessels. Churg and Strauss,[12] in reviewing autopsies in 10 cases of asthma associated with polyarteritis, described granulomatous lesions in the lungs associated with eosinophilia and necrotizing arterial lesions. Rich [50,51] indicated that the lesions of periarteritis nodosa were manifestations of an anaphylactic type of hypersensitivity. The demonstration in this paper of a granulomatous and eosinophilic process accompanied by arteriolar inflammation, necrosis, and fibrosis seems to indicate a relationship between this condition and periarteritis nodosa.

Little attention has been given to the possibility that the condition being discussed might be a variation of Loeffler's syndrome. Although many clinical data are available,[17, 25,32] pathologic studies are few,[5,6,8,10,27,43]

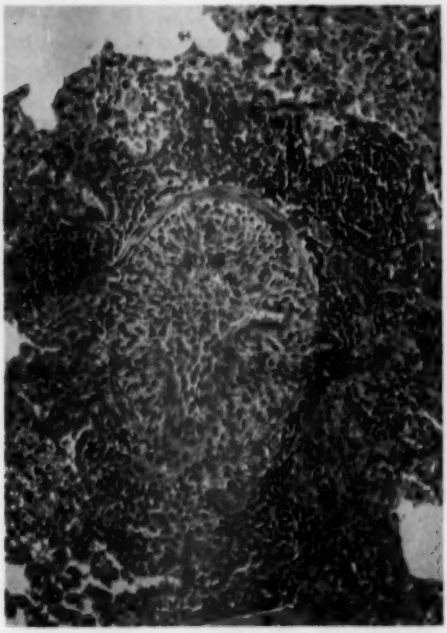


Fig. 17 (Case 1).—Bronchiole infiltrated and occluded by histiocytes. Hematoxylin and eosin; reduced to 60% of mag. × 225.

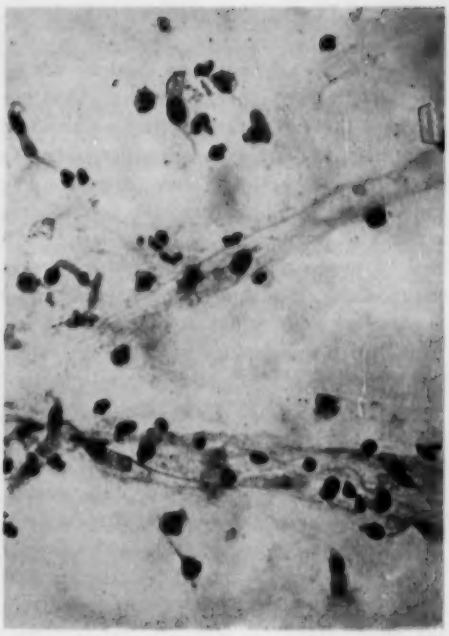


Fig. 18 (Case F1).—Eosinophils in bronchial washings. Hematoxylin and eosin; reduced to 60% of mag. × 765.

due to the general benignancy of the disease. Some of the cases autopsied did not show proof of the migratory nature of the pulmonary infiltrate. Most of the reports described tissue eosinophilia and consolidation of a part of the pulmonary tissue by inflammatory exudate, fibrosis, or granulomas; interstitial pneumonitis and necrotizing arteritis were often noted. The bronchial changes characteristic of asthma were observed in most of the cases. Bayley, Lindberg, and Baggenstoss [5] described fibrosis and the formation of tubercle-like lesions composed of histiocytes surrounded by inflammatory cells in the center of which was a mass of acidophilic granular necrotic debris. They also described thickening, inflammation, and necrosis of arterial walls. They concluded that many of the lesions were not transient; the fibrinoid swelling and necrosis of collagen suggested an allergic basis for the disease, and the necrotizing arteritis and arteriolitis histologically resembled the changes in periarteritis nodosa. Harkavy [27] found lesions of periarteritis in his cases, and Buckles and Lawless [10] described a periarteritis and arteriolitis with eosinophilia, as well as granulomatous and fibrotic areas infiltrated with eosinophils. None of these papers reported parasites in the tissues, and a number of different etiologic agents have been discovered.[35]

Thus the basic pathologic changes in eosinophilic granuloma of the lung, periarteritis nodosa, and Loeffler's syndrome appear to be related. We might interpret eosinophilic granuloma of the lung as a chronic response to a low-grade antigen (probably an inhalant, because of its diffuse pulmonary distribution), while Loeffler's syndrome would represent a more acute reaction with larger areas of the lung responding at one time to the stimulus. The transient and recurring nature of the lesions in eosinophilic granuloma of the lung has been pointed out, and these may actually represent Loeffler's infiltrations in miniature—too small, too

diffuse, and too quickly replaced to be recognized as transitory.

Finally, the above views must be reconciled with the overwhelming evidence linking the condition with eosinophilic granuloma of bone, Hand-Schüller-Christian disease, and Letterer-Siwe disease. The unity of the last three has been conclusively proved by Lichtenstein [37] and others.[18,20,24,26,31] I agree that these do not represent xanthomas per se, but that the lipoid phase is merely coincidental to tissue necrosis. The British terminology of cystic or honeycomb lungs [13,34,46,48] is picturesque but vague. Some of the cases described under that heading probably fall into the Hand-Schüller-Christian or eosinophilic granuloma group. Many cases of eosinophilic granuloma of bone have shown a diffuse pulmonary infiltrate by x-ray, and several papers [11,40] have demonstrated similar histopathology in bone and lung lesions from the same patient. Arteriolitis may be found in the bone condition.

If a hypersensitive state is assumed as the comon denominator for all these disorders, we are able to correlate the findings in eosinophilic granuloma with the other conditions. Hypersensitivity does not seem too unlikely. Bacteriologic, mycotic, and parasitic causes have been ruled out; the reticuloendothelial system seems to be responding to a stimulus of some sort, and beneficial effects of steroids [7,23,29] and x-radiation [14,18,30,49] have been reported; granuloma formation and tissue eosinophilia of some degree have been recognized in all these disorders. Eosinophilic granuloma of the lung, on the one hand, may indicate the tissue response to an antigen in the height of its activity, corresponding to Loeffler's syndrome and periarteritis nodosa (Figs. 5, 12); this may be the essential feature of the first, or "hyperplastic-proliferative," stage of the process, as outlined by Engelbreth-Holm et al.[18] On the other hand, it also shows the granulomatous and fibrotic phases (frequently in the same specimen) more characteristic of Hand-Schüller-Christian disease (Figs. 10, 11). The xanthoma proper with nests of foam cells is not often seen in eosinophilic granuloma of the lung, probably because the material has been carried away through communications with the bronchi.

Summary

Pulmonary eosinophilic granuloma was first described in 1951, and its relationship to eosinophilic granuloma of bone was recognized. The latter condition was reported in 1940, and since that time numerous cases have been reported, some of which showed pulmonary lesions by x-ray. With the first reports, the similarity of the condition to Hand-Schüller-Christian disease was suggested, and subsequent papers have shown that eosinophilic granuloma, Hand-Schüller-Christian disease, and Letterer-Siwe disease are all variations of the same basic disorder. Lichtenstein called the process "histiocytosis X."

Following the initial description of eosinophilic granuloma in the lungs, several papers appeared with pathologic studies of the process, most of the specimens having been obtained for biopsy. No autopsy has been performed in these cases, and one can only infer that the process is not a generalized one. In some of the cases the pulmonary involvement was the only manifestation of the disease; a few had associated eosinophilic granulomatous lesions of bone, and two had symptoms suggestive of the Hand-Schüller-Christian syndrome.

Three new cases are reported in this paper in which the lungs were the only organ affected by the disease. The first patient was 20 years old and complained of chest pain and dyspnea. His chest roentgenogram showed a bilateral nodular infiltration which was suggestive of Boeck's sarcoid, and the past history showed that he had broken a barrelful of fluorescent light tubes four years previously. An exploratory thoracotomy was done, and the tissue examination revealed eosinophilic granuloma. No specific therapy was given, and the patient was alive and well 19 months after the operation.

The second patient complained of pneumothorax, and the x-ray film showed a diffuse pulmonary infiltration. An old film taken two and one-half years previously showed the same process, but less marked, whereas the patient was asymptomatic. No diagnosis could be made, and a thoracotomy was done. The pathologic diagnosis was eosinophilic granuloma of the lung. Pneumothorax continued after the operation, but after an intensive course of steroid therapy the patient became relatively asymptomatic. One and one-half years after operation the patient was improved and able to work.

The third patient had a chronic cough, weight loss, and right spontaneous pneumothorax, and a roentgenogram revealed a diffuse bilateral pulmonary nodular infiltration. Exploration of the right thoracic cavity was done, and a diagnosis of eosinophilic granuloma was made. Roentgen therapy to the lungs resulted in some clearing of the infiltrate, and six months later the patient was considerably improved.

A clinical picture of the process is drawn from the 3 cases reported herein and the 10 reported elsewhere. Most of the patients were young Caucasian men. The clinical course is usually mild except in those cases with pneumothorax. Four of the thirteen had this symptom. Other complaints are usually cough, dyspnea, mild chest pain, and some weight loss. Chills, fever, and night sweats are seldom seen. Some degree of malaise and fatigability is found.

The physical examination is generally negative except for a few rales in the chest. Those cases with pneumothorax show the signs characteristic of that symptom. The leukocyte count is usually elevated, and occasional cases may show a mild eosinophilia. The sedimentation rate is elevated, and the serum globulin is increased in some patients. The chest roentgenogram shows a diffuse bilateral infiltrate, and occasional blebs or cysts may be found in the lung or on the pleura.

Treatment of the condition with steroids and x-radiation has shown promising results. All of the cases improved with or without therapy, but roentgenographic cleaning of the lungs occurred only with treatment.

The gross pathologic anatomy was compiled from the surgeons' observations, as most of the material consisted only of small biopsy specimens. Most of the descriptions reveal a diffuse granular or nodular infiltration in the lungs. The pleura may be involved by the lesions, and in some instances blebs are found on the surface. Rare pleural adhesions were found, but no pleural effusion was seen.

Microscopically the lesions consist of multiple granulomatous processes. Eosinophilic infiltration is heavy in many instances, and the surrounding alveolar septa show an interstitial inflammation. The inactive lesions are free of eosinophils, and the surrounding tissue is normal. Many of the arterioles are acutely inflamed, and eosinophils are found throughout the thickness of the wall. Acidophilic degeneration may be found in the adventitia. The older lesions may undergo necrosis as the blood supply is impaired, and the mass may be extruded into the bronchi. In other instances fibrous tissue may replace the nodule, resulting in a scar.

A possible relationship of the process to infections, parasitic infestations, and granulomas, like Hodgkin's disease, berylliosis, and sarcoidosis, seems to be ruled out by the pathologic findings and the clinical course, but evidence is presented which indicates the disease may be a hypersensitive state. There are a necrotizing arteriolitis, a heavy eosinophilic infiltration, occasional elevated globulin, and peripheral eosinophilia. The lesions resemble those of periarteritis nodosa, as well as those found in the few cases of Loeffler's syndrome which were studied pathologically. The improvement with steroid therapy tends to substantiate the theory.

This hypothesis is not inconsistent with the fact that the process is related to "histiocytosis X," and eosinophilic granuloma may be an active, but chronic, stage of a

little understood condition that basically is a state of hypersensitivity.

2750th U. S. A. F. Hospital, Wright-Patterson AFB, Dayton, Ohio.

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Diffuse Interstitial Pneumonitis; Acute, Fibrosing, and Focal Healing Patterns

Etiology and Malignant Potentiality

K. R. CROSS, M.D., Iowa City

The pathology of the lungs which we see in our daily practice is changing. This is true in part because the surgical procedure of thoracotomy with biopsy, lobectomy, or pneumonectomy makes available for examination diseases of these organs in stages of development rarely seen prior to 10 years ago. The use of antibiotics accounts in part for this change, by the control of some entities and by control of the bacterial element alone in other conditions. The diagnosis of primary atypical pneumonia, assumed by the majority to be a viral disease, was reintroduced in the current literature in 1940 by Kneeland and Smetana.[1] Since then the incidence of this condition has increased tremendously. We are currently seeing also a significant increase in the incidence of so-called diffuse fibrosing interstitial pneumonitis. This has been recognized as a distinct entity since the original description, in 1944, by Hamman and Rich,[2] in which they reported four cases, three of which had come to their attention earlier. Solitary and multiple pseudotumors of the lungs and pleurae have also been described with much greater frequency. These have been variously classified. The relative incidence of hamartomas, called mixed tumors by some, has also increased and accounted for 16% of solitary lesions of the lungs removed from 156 patients in one series recently reported,[3] in which three, or 1.9%, were classified as mesotheliomas.

Submitted for publication May 21, 1956.

From the Departments of Pathology, Veterans Administration Hospital, and State University of Iowa College of Medicine.

The incidences of these conditions, namely, (1) acute interstitial pneumonitis (virus pneumonia, atypical pneumonia), (2) diffuse fibrosing interstitial pneumonitis (diffuse interstitial fibrosis, acute and chronic, or the Hamman-Rich syndrome), with and without conspicuous pleuritis, and the (3) single or multiple focal lesions of the lungs and pleura (pseudotumors, fibromas, mixed tumors, some hamartomas, and mesotheliomas) have paralleled one another in their increase, an incidence which, aside from that of bronchiectasis and bronchial neoplasm, virtually dominates the field of pulmonary pathology.

In the literature, and in the experience of my colleagues and myself, I have been impressed with the latitude of each of these conditions, which have been regarded as distinct entities. Considerable overlapping is apparent. The volume of terminology and speculation which has accumulated supports this observation also.

Final proof that these forms represent progressive intervals of the same process must await clear demonstration of the etiology, which at this time is lacking in all of them. In this paper, however, I would like to present 7 cases selected from more than 30 of these types which have concerned us in these hospitals, each of which would qualify under one or more titles in current use. Their progressive and overlapping characteristics will be emphasized. The first case is that of an acute situation which was rapidly fatal (Case 1). We shall progress to a less acute, but nonetheless severe and fatal, illness (Case 2). This will be followed by a consideration of more

slowly progressive diseases of the lungs and pleura (Cases 3, 4, and 5), in all of which focal lesions of the lungs or pleura or both were becoming prominent. In all these cases residuals of more generalized disease remained. Finally, cases of nearly healed "focal lesions" of the lung will be presented (Cases 6 and 7), in which, after surgery, there were also found several small focal lesions, mild continued activity, and the pulmonary scars of old disease. These representative cases seem to bring together into a common pathologic entity many lesions which have been variously separated and classified in the range of titles cited above.

In the discussion, I shall point out what I consider to be some of the significant observations by ourselves and others regarding the etiology of this at times progressive and long-drawn-out condition.

I would also like to reemphasize the fine line of distinction between these lesions and malignancy. The differentiation is recognized as difficult to make clinically, roentgenographically, and grossly. On microscopic examination, also, areas of anaplasia are often indistinguishable from neoplasia, particularly if the pathologist is confined to the examination of a single slide, without additional information. This wild anaplasia —which we may one day learn to identify as precancerous, or even early malignancy— was demonstrable in some of these patients.

Report of Cases

CASE 1.—This 29-year-old white man was in good health until 25 days before admission to this hospital, at which time he developed a "cold" and began to cough up yellowish, mucoid material which was blood-streaked. An x-ray of the chest, taken at that time and subsequently reviewed, revealed an area of homogeneous density in both lower lung fields. The productive cough worsened, with greater hemoptysis and insomnia. About 22 days after the onset extreme weakness developed, with dehydration and a sense of constriction in the throat and chest. On the day of admission discomfort was noted for the first time in the left chest.

He was very ill, pale, and weak and coughed spasmodically. The temperature was 99.6 F and the pulse rate 120 a minute. The WBC count was 12,100; the RBC count 2,090,000, and the Hb 6 gm. per 100 cc. The differential count was within normal limits. The roentgenologist reported bilateral parenchymal infiltration throughout both lung fields (Fig. 1, upper left).

Bacteriologic examinations of sputum revealed no acid-fast bacilli or fungi, but α- and β-hemolytic streptococci, and a few nonhemolytic Staphylococcus aureus organisms were cultured. The same organisms were recovered from throat smears.

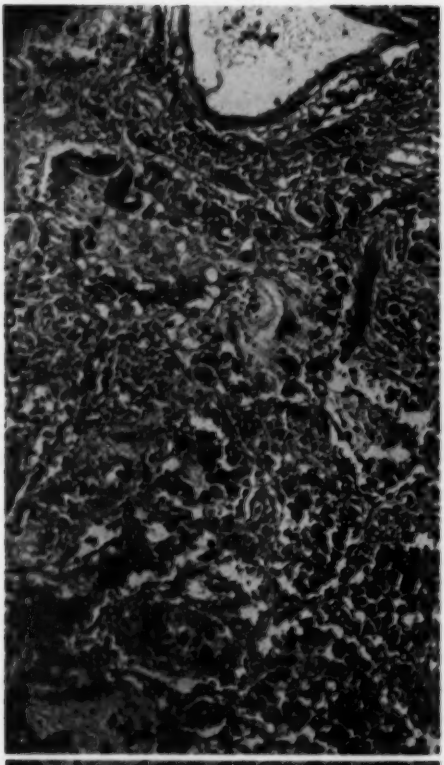
The patient rapidly became more ill, restless, and disoriented. He was given 500 cc. of blood followed by saline, and antibiotics were started. After four hours greater dyspnea and tachycardia were apparent, along with increasing paleness and beginning cyanosis. Nine hours after admission sudden profuse hemoptysis began, and he died an hour later.

There was approximately 200 cc. of blood-tinged fluid in each pleural space. The right lung weighed 1600 gm. and the left 1200. The tracheobronchial tree contained both old and fresh blood. The pleural surfaces were smooth, finely lobulated, and dark, due to the underlying congestion and hemorrhage (Fig. 1, lower left). The lungs were firm and almost airless. The cut surfaces were finely granular, and the lobules bulged slightly. The coloration of old and recent hemorrhage was apparent.

Microscopically, many alveoli were filled with fresh blood; some, with hemolyzed blood, and some contained phagocytes filled with blood pigment (Fig. 1, upper right). Some contained fibrinous material, which appeared to line them. Alveolar walls were thickened, due to capillary dilatation, mononuclear infiltration, and intense hyperplasia of lining cells and connective tissue (Fig. 1, lower right). This hyperplasia approached early scarring in some areas. Bronchiolar epithelium was extremely hyperplastic, with many hyperchromatic nuclei and a few mitoses. Bronchioles were surrounded by many lymphocytes and a few neutrophiles.

Cultures for bacteria and fungi were made from heart blood, lymph nodes, and portions of lung tissue. No pathogenic organism was isolated.

The viral studies in this case were performed in two separate laboratories. A 10% suspension of lung tissue was passed in chick embryos, the embryos dying on the first and second passages, on the fourth or fifth day after inoculation, but not dying on the third passage. No etiologic agent, viral or rickettsial, could be definitely dem-



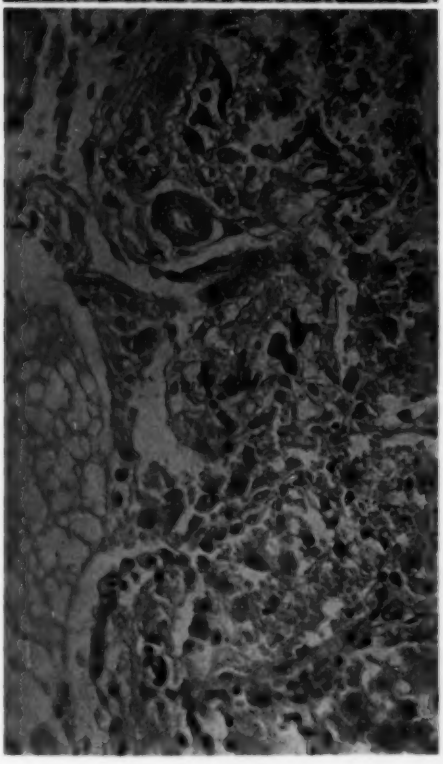


Fig. 1 (Case 1).—Upper left: chest x-ray, showing parenchymal infiltration throughout both lung fields.

Lower left: Right lung, weighing 1600 gm., which was firm and airless. Note the finely lobulated surface and the evidence of old and recent hemorrhage.

Upper right: lung. Old and recent hemorrhage with round-cell infiltration of peribronchiolar and septal tissue and of alveolar walls. Hematoxylin-eosin; × 120.

Lower right: lung. Old hemorrhage and older inflammation with fibrinous intra-alveolar material. Note the mononuclear-cell infiltration and extreme hyperplasia of connective tissue and alveolar lining cells. Hematoxylin-eosin; × 245.

onstrated by observation of stained smears prepared from tissue of the chick embryo, or by way of immunologic procedures.

It was concluded, on the basis of total examination, that death resulted from an acute interstitial pneumonitis, intra-alveolar hemorrhage occurring at intervals over a period of 26 days, with massive intrapulmonary hemorrhage shortly before death. The cause of this pneumonitis has not been positively determined, but the disease is thought to be of viral or rickettsial origin.

CASE 2.—The disease in this 58-year-old man involved all lobes of both lungs. He stated that he had had influenza in 1918, but a long interval of apparent good health followed.

In the eight years since symptoms of lung disease first appeared, he had been examined extensively and treated symptomatically for variable periods of time in four excellent hospitals and clinics in the United States. He had a severe cough, was dyspneic and weak, and was losing weight. Respirations were shallow and rapid. Crackling rales were heard over both lungs, and he was mildly cyanotic. The sedimentation rate was elevated; there was mild leukocytosis; the differential count was within normal limits, and the vital capacity was reduced to 30% of normal. Only staphylococci, streptococci, and Hemophilus organisms, all sensitive to antibiotics, were recovered from the lungs. By x-ray (Fig. 2, upper left), diffuse, nodular infiltration of all lobes of both lungs was demonstrated. The bronchoscopist could see only chronic bronchitis but was impressed with the rigidity of the tracheobronchial tree. Antibiotic and supportive therapy was given, but the patient worsened to death, 20 days after admission to the hospital.

There was subacute, diffuse, productive pneumonitis of such severity that the patient died of pulmonary insufficiency. The lungs were firm and weighed 885 and 860 gm. respectively. The surface was finely nodular (Fig. 2, middle left). On cut section they appeared firm, gray, and relatively dry. Both diffuse and more focal zones of grayish-white scarring were seen.

Sections from all lobes of both lungs were similar, with many zones of complete scarring infiltrated with lymphocytes, plasma cells, and large mononuclear cells. There was exuberant hyperplasia of bronchiolar and alveolar epithelium (Fig. 2, lower left) with moderate to severe anaplasia. In a few areas there was fibrinoid degeneration in zones of dense scarring. In the areas of least involvement (Fig. 2, upper right), there was both diffuse and nodular thickening of the alveolar walls and septa, due to connective tissue hyperplasia and scarring, with hyperplasia and anaplasia of alveolar lining cells. Hilar nodes were firm and moderately enlarged. In two of them, several zones of fibrinoid degeneration mingled with intense retothelial hyperplasia and giant-cell formation were seen (Fig. 2, middle right). These foci blended with surrounding hyperplastic tissue of the lymph nodes without a marginal reaction.*

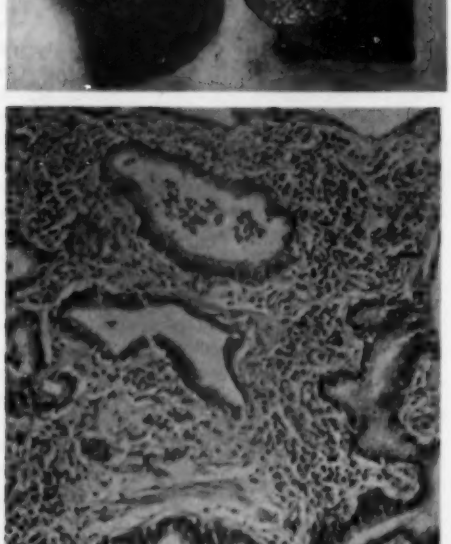
Studies utilizing direct smears, cultures for ordinary bacteria, Mycobacterium tuberculosis, and fungi, and special stains of tissue failed to reveal organisms other than those isolated clinically. There was no growth from several specimens collected aseptically from various areas of lung at the time of autopsy.

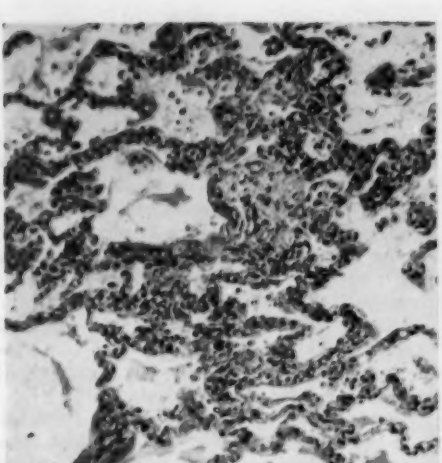
Case 3 serves to bridge the gap between the lesions of the lung parenchyma and those of the pleura.

CASE 3.—The 60-year-old man had had pneumonia 40 years ago. Six months before admission he noted the gradual onset of pain in the left chest and flank. He raised a small amount of whitish sputum, without hemoptysis. He had had no febrile reactions, to his knowledge. During the six-month period, he had lost 50 lb. (22.7 kg.) in weight, and thoracenteses had been performed six times.

When he was admitted to the hospital, the temperature and blood pressure were within normal limits. The pulse rate was 110 a minute. The left chest expanded poorly, and breath sounds were diminished. There was slight elevation of the white cell count, but other laboratory findings were within normal limits. Repeated thoracenteses were performed, and many examinations of direct preparations and by cultural methods for bacteria, including M. tuberculosis and fungi, were negative. After many thoracenteses, x-rays revealed the left lower lobe to be collapsed, with a rigid appearance as though encased in thick fibrous tissue. Considerable fibrosis was noted about the left upper lobe, as well as linear interstitial fibrosis. Nodular and focal areas of infiltration were noted in the midportion of the right lung near the periphery. These areas were round with irregular borders and measured up to 6 mm. in diameter (Fig. 3, upper left). On bronchoscopic

* Regional nodes bearing this pattern of sarcoid have been observed by me in three other cases of acute and fibrosing interstitial pneumonitis. One of these cases had diffuse interstitial myocarditis (Fiedler's myocarditis) as well. It has also been observed twice at the University Hospital in cases of this type.[4]





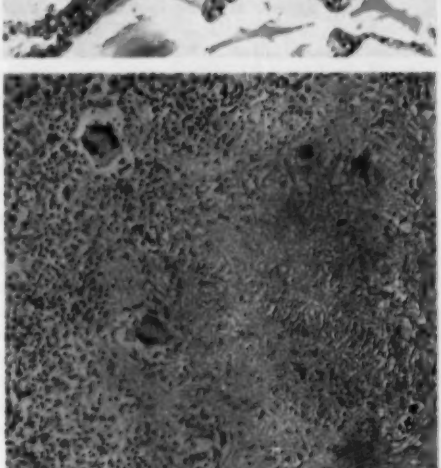


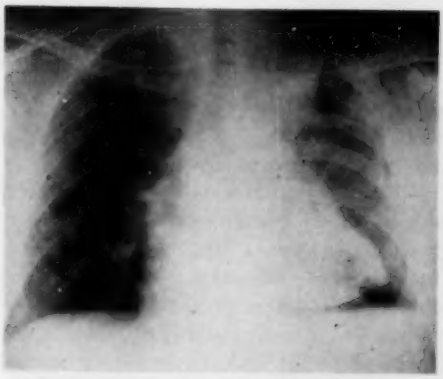
Fig. 2 (Case 2).—Upper left: chest x-ray, showing diffuse and nodular parenchymal infiltration of all lobes of both lungs.

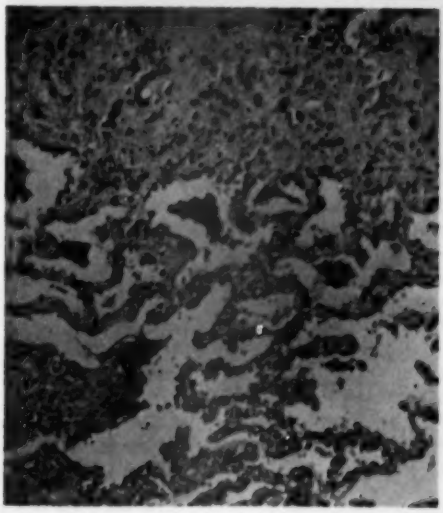
Middle left: lungs, having a combined weight of 1745 gm. The surfaces are finely nodular, and they were extremely firm.

Lower left: lung. Extreme hyperplasia, with moderate to severe anaplasia of bronchiolar epithelium and alveolar lining cells. Hematoxylin-eosin; × 120.

Upper right, area of least involvement from these lungs, in which there are still diffuse and nodular fibrosis and alveolar-lining-cell hyperplasia and anaplasia. Hematoxylin-eosin; × 120.

Middle right: hilar lymph node with focus of fibrinoid degeneration, mingled with retothelial hyperplasia and giant-cell formation. Hematoxylin-eosin; × 120.





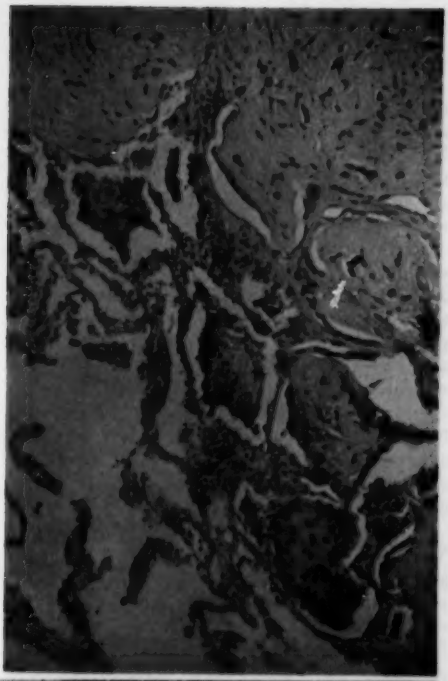


Fig. 3 (Case 3).—Upper left: chest x-ray, showing collapse of left lower lobe with pleural thickening, as well as linear and nodular interstitial fibrosis.

Middle left: left lower lobe, showing the irregularly thickened pleura, parenchymal fibrosis, and beginning "pseudotumors" of pleura and lung parenchyma.

Lower left: pleural mesothelium, above, and alveolar lining cells, below, participate indistinguishably in the formation of the "pseudotumors." Hematoxylin-eosin; × 120.

Upper right: Individual alveolar masses fuse to form relatively acellular "tumors." Hematoxylin-eosin; reduced to 47% of mag. × 50.

Middle right: focal "pseudotumor" being formed at all margins by the keloid-like product of alveolar lining cells. Hematoxylin-eosin; reduced to 84% of mag. × 7.

examination, the orifice to the left lower lobe appeared narrowed, without evidence of neoplasm. Examination of bronchial aspirations and washings for tubercle bacilli and fungi were negative. Examination of cell clumps by the centrifugation and sectioning technique, which others and I have described,[6] revealed small cell masses showing squamous metaplasia and anaplasia, reported as 3+, suggestive (1+ to 5+) of malignancy. With these inconclusive findings, a left thoracotomy was performed. Part of the dense pleura was removed from both lobes. The lower lobe could not be expanded, however, and it was removed. Postoperative empyema developed, from which hemolytic S. aureus was recovered. With drainage and antibiotic therapy this improved. Under hospital management he gained weight and his general condition improved slowly.

The lower lobe of the left lung weighed 180 gm. The bronchial mucosa was slightly thickened and granular, but no focal changes were apparent. The pleura was firm, grayish-white, and greatly thickened (up to 4 mm.) in an irregular fashion (Fig. 3, middle left). When the lung was cut, the parenchyma also was seen to be firm, and many small foci of gritty fibrosis were encountered. Some of these were somewhat translucent, and the largest measured 1.3 cm. in diameter (Fig. 3, middle left).

Microscopically, in the areas of lung parenchyma having least involvement, there was thickening of alveolar walls, due to hyperplasia and fibrosis. There were small foci of lymphocytic infiltration, with scarring about vessels and bronchioles (Fig. 3, lower left). There were hyperplasia of bronchiolar and alveolar lining cells and often considerable anaplasia, which was even greater than that observed in Cases 1 and 2.

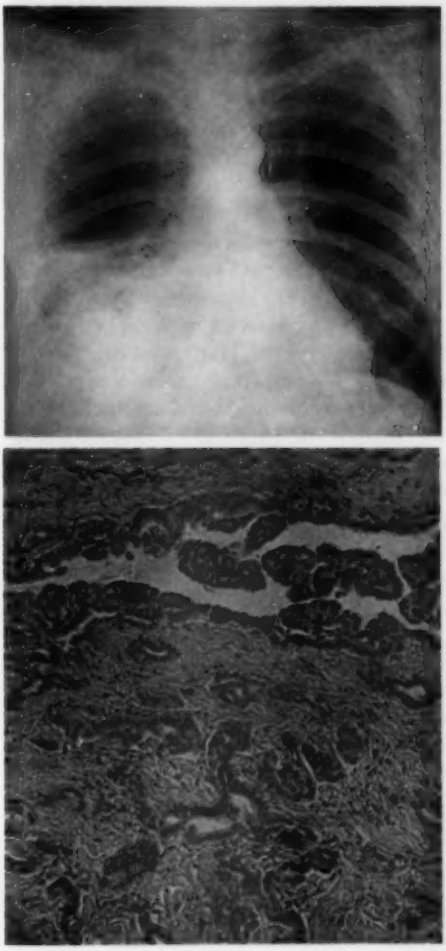
In the majority of sections of lung parenchyma there were many poorly defined zones of hyperplasia of the lining cells of alveoli. In these areas a homogeneous matrix was often deposited, which stained light pink or bluish, resembling chondromucin. Nuclei were entrapped in the latter material (Fig. 3, upper right). This was continuous with obvious collagenous material. Clearly, alveolar lining cells became hyperplastic and entrapped themselves in a structureless matrix, which first filled the alveoli and then fused with those adjacent to it. Toward the center of larger nodules, the nuclei disappeared and a relatively anuclear, keloid-like pseudotumor remained. (A later stage of this tumor is exemplified in Case 6, and a still later one, which is nearly quiescent, in Case 7.) When these "tumors" were in contact with pleura, the latter participated in their growth. In zones remote from these "tumors" the mesothelia cells became rounded up and were present as alveoli, cells strands, and masses. Adjacent to them, similar cartilaginous and collagenous material was produced (Fig. 3, upper right). The mechanism of production seems to be the same whether the "tumor" was in parenchyma, or in pleura or in both. In many areas the zones of fibrosis were much larger and amounted to the "fibromas," "myxomas," or pseudotumors of the literature (Fig. 3, middle right).

Seven months after surgery, roentgenograms showed that the linear fibrosis in lungs had increased and the focal nodules increased slightly in size. It seemed inevitable that pseudotumors of both lungs and pleurae were forming in other zones of this patient's chest. During the subsequent two years, however, there has been little, if any, change.

In these next two cases, the disease was manifest particularly in the visceral pleura at the time of first examinations. Microscopically, however, lung parenchyma was similarly involved.

Case 4.—This 46-year-old man was told he had disease of the right lung when he was examined for discharge from the Army, seven years before this hospitalization. He denied pulmonary symptoms at that time but was hospitalized for three months for possible tuberculosis. He was operated on and was told that a "hole in the lung had been repaired," but he received no further information. During the years following he noted increasing shortness of breath, weakness, and fatigue. Four months before admission, "4½ quarts" of fluid was removed from the right chest. One month before admission another thoracentesis yielded "2 quarts" of fluid.

After admission, thoracentesis was performed several times. Bacteriologic studies of sputum and thoracentesis fluid failed to reveal the cause of the dense pleuritis of the entire right side, which was demonstrated on x-ray (Fig. 4, upper left). All laboratory studies were within normal limits.



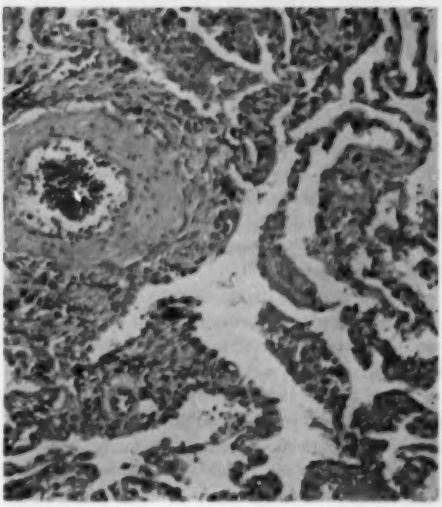


Fig. 4 (Case 4).—Upper left: chest x-ray, showing the dense pleuritis of the right lung.

Upper right: right lung. Note the nodular, dense pleuritis and parenchymal fibrosis.

Lower left: pleura. Note the extreme mesothelial-cell hyperplasia and the dense stroma with which it is continuous (cf. Case 3). Hematoxylin-eosin; × 120.

Lower right: lung parenchyma. There are great hyperplasia, round-cell infiltration, and scarring. Pseudotumors, comparable to those in Case 3, were making their appearance in some zones. Hematoxylin-eosin; × 120.

A decortication of the lung was performed. The lung did not—or could not—reexpand, and pneumonectomy and thoracoplasty were subsequently carried out. Bacteriologic examinations and special stains of the lung failed to reveal an etiologic agent. Diphtheroids were found as contaminates.

In the pleural peel there was an intense, chronic desmoplastic reaction. Wildly infiltrating the hyperplastic connective tissue were strands and acini of anaplastic mesothelium. The latter varied from one area to another, being secretory in appearance with vacuolation of cytoplasm in one location,

and with cuboidal cells in others, showing early squamous changes in some areas (Fig. 4, lower left), and being made up of fusiform, sarcoma-like cells in still others. Anaplasia was manifest by moderate anisonucleosis, numerous hyperchromatic nuclei, and a few mitoses (Fig. 4, lower left).

The lung, removed at the second operation, weighed 445 gm. and was virtually encased in firm, grayish-white, nodular material, which measured up to 4 mm. in thickness (Fig. 4, upper right). On cut section there was diffuse and mottled scarring, with firmness and loss of elasticity.

Microscopically, there were considerable peribronchial and perivascular fibrosis, thickening of septal walls due to fibrosis (Fig. 4, lower right), and numerous small nodular scars containing a few lymphocytes. There was great cuboidal hyperplasia of bronchiolar and alveolar lining cells, which were continuous with those infiltrating the thickened pleura and covering its surface (Fig. 4, lower left).

CASE 5.—This 61-year-old white man entered the hospital because of increasing shortness of breath during the prior two weeks. He had had pneumonia in 1918. He had had a chronic cough for many years, with an occasional trace of blood in the sputum. He had moderate orthopnea. The temperature was normal. There was decreased expansion and dullness over the right chest. X-rays revealed a right pleural effusion, which was drained. No fungi or bacteria were recovered, in several attempts. Streptokinase-streptodornase (Varidase) was used but the lung failed to expand, and 17 days after admission decortication of the right middle and lower lobes was performed. A bronchopleural fistula developed. At reoperation the fistula was closed and additional pleural peel removed. Mild empyema developed, from which hemolytic S. aureus and Pseudomonas aeruginosa organisms were recovered. The patient improved gradually and was discharged from the hospital, with partial reexpansion of the lung.

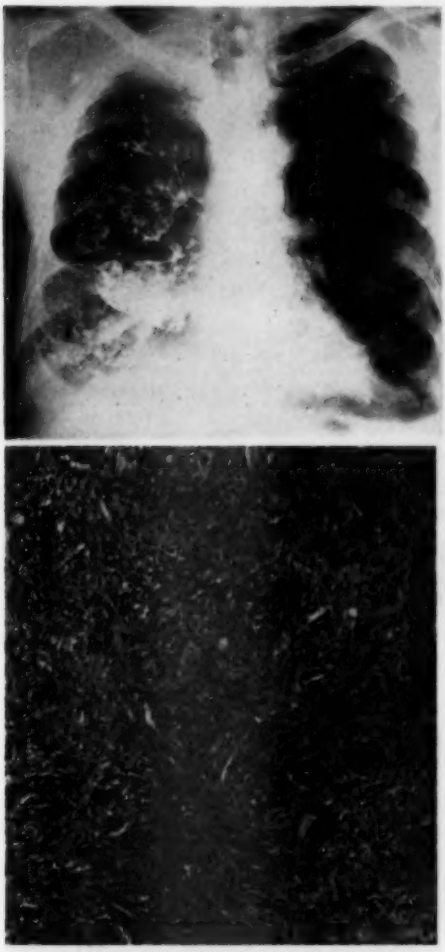
Preoperative x-rays demonstrated (right bronchogram, Fig. 5, upper left) partial collapse of the right middle and lower lobes. They appeared to be encased in thickened pleura, which was most prominent at the base but which extended to cover the apex. Linear and interstitial fibrosis was present throughout both lungs. Two large emphysematous blebs were present in the left upper lobe.

The pleural peel removed at the first operation consisted of chronic granulation tissue with active connective tissue and endothelial hyperplasia (Fig. 5, lower left). There were also strands and acini of epithelial-like tissue. Significant anaplasia was not apparent, and there was light lymphocytic infiltration. Pulmonary tissue was not included. In the second specimen there was a great amount of pseudoglandular, epithelial-like tissue, showing extreme hyperplasia and anaplasia (Fig. 5, upper right). Marginal pieces of lung parenchyma were included. These actually were too close to the pleura to be considered definitely representative of the condition of lung parenchyma generally, but there was irregular thickening of septa due to scarring and hyperplasia of all elements. Fibrinoid material was present in the alveoli, and there were definite hyperplasia and anaplasia of lining cells.

At the time of writing, five months after surgery, roentgenograms are reported to show little essential change in the linear fibrosis. A small, hazy nodule has made its appearance in the right upper lobe, however. At this time the patient feels well, has maintained his weight, and has no complaints.

As one might expect after seeing the photographs in this case, individual areas were considered highly suspicious of malignancy. Inspection of the total specimen and evaluation of the underlying disease, however, prompted a diagnosis of chronic pleuritis in association with chronic interstitial pneumonitis. The clinical course of the patient more than a year later substantiates that diagnosis, and the microscopic findings are of the same type as those seen in the other cases.

The last two cases represent further progression of this disease. In the first (Case 6) there was pleural and parenchymal involvement combined with a "tumor" mass. In the last (Case 7) the pleura was scarred, but the "tumors" did not attach to it. In the first there was still moderate marginal



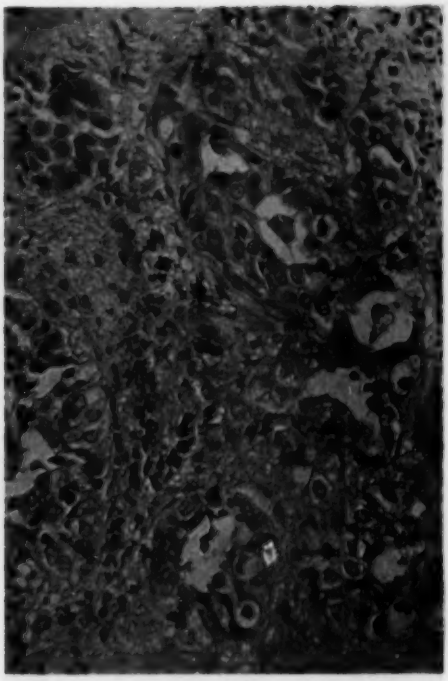


Fig. 5 (Case 5).—Upper left: right bronchogram. There is partial collapse of the middle and lower lobes with dense pleuritis. Linear and interstitial fibrosis is present in both lungs.

Lower left: pleura. Chronic inflammatory tissue with severe hyperplasia and scarring. Hematoxylin-eosin; × 120.

Upper right: pleura. Higher magnification, showing the adenocarcinoma-like features to which this anaplasia may progress. Hematoxylin-eosin; × 300.

activity, and in the last it was mild. In both cases the scarring of diffuse interstitial pneumonitis was evident.

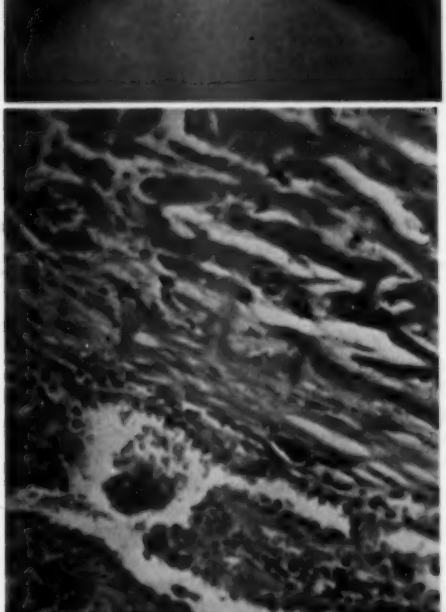
Case 6.—At the age of 15, a mass in the right lower lung field was demonstrated when the patient was x-rayed in the course of a chest survey program. The mass was sharply circumscribed and was said to be located about 2 cm. above the dome of the diaphragm (Fig. 6, upper left). This area was frequently reexamined and did not change appreciably. There was no symptoms of chest disease. Removal was recommended because of the possibility of future malignant changes, and this was accomplished two years after discovery of the mass.

At operation, a mass measuring 7 cm. in diameter was found in the right lower lobe; the tumor was fused to the esophagus and pericardium. It was freed from these structures by dissection and resection of portions of pericardium and esophageal musculature. The lower and middle lobes of the lung were removed.

There was one large mass, and several smaller satellite ones were present along its superior border. It was hard and not encapsulated. When cut, it was grayish-tan in color, had a whorled configuration, and contained irregular calcification in the center.

Microscopically, the mass was made up of broad bundles of fibrous and fibroblastic tissue. There were relative acellularity and calcification in the central zone. At the margins (Fig. 6, lower left) the growth

radiated into adjacent tissue, with extension of fibrosis into septa and alveolar walls. There was active hyperplasia of bronchiolar epithelium and alveolar lining cells at the margins, and many acinar-like alveoli were entrapped in fibrous tissue. In the marginal zone, bronchioles and vessels were likewise surrounded and compressed (Fig. 6, lower right). There was rather heavy infiltration by lymphocytes, plasma cells, and large mononuclear cells. There were mild, irregular thickening of septa and alveolar walls and hyperplastic changes in lung tissue well removed from these focal lesions.



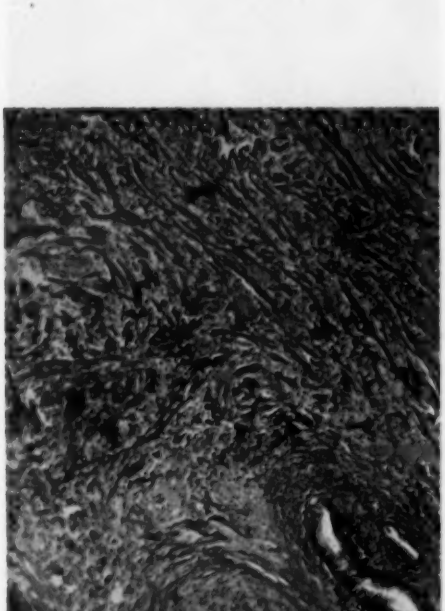


Fig. 6 (Case 6).—Upper left: chest x-ray. Note the conglomerate "pseudotumors" in the right lower lobe, which were fused to diaphragm and esophagus.

Lower left: the keloid-like "pseudotumor," above, merges with adjacent pulmonary tissue. There is hyperplasia of alveolar lining cells and their participation in tumor formation and interstitial fibrosis. Hematoxylin-eosin; × 160.

Lower right: another marginal zone in which hyperplastic alveolar cells contribute to "pseudotumor" and fibrosis, with choking of bronchioles. Hematoxylin-eosin; × 120.

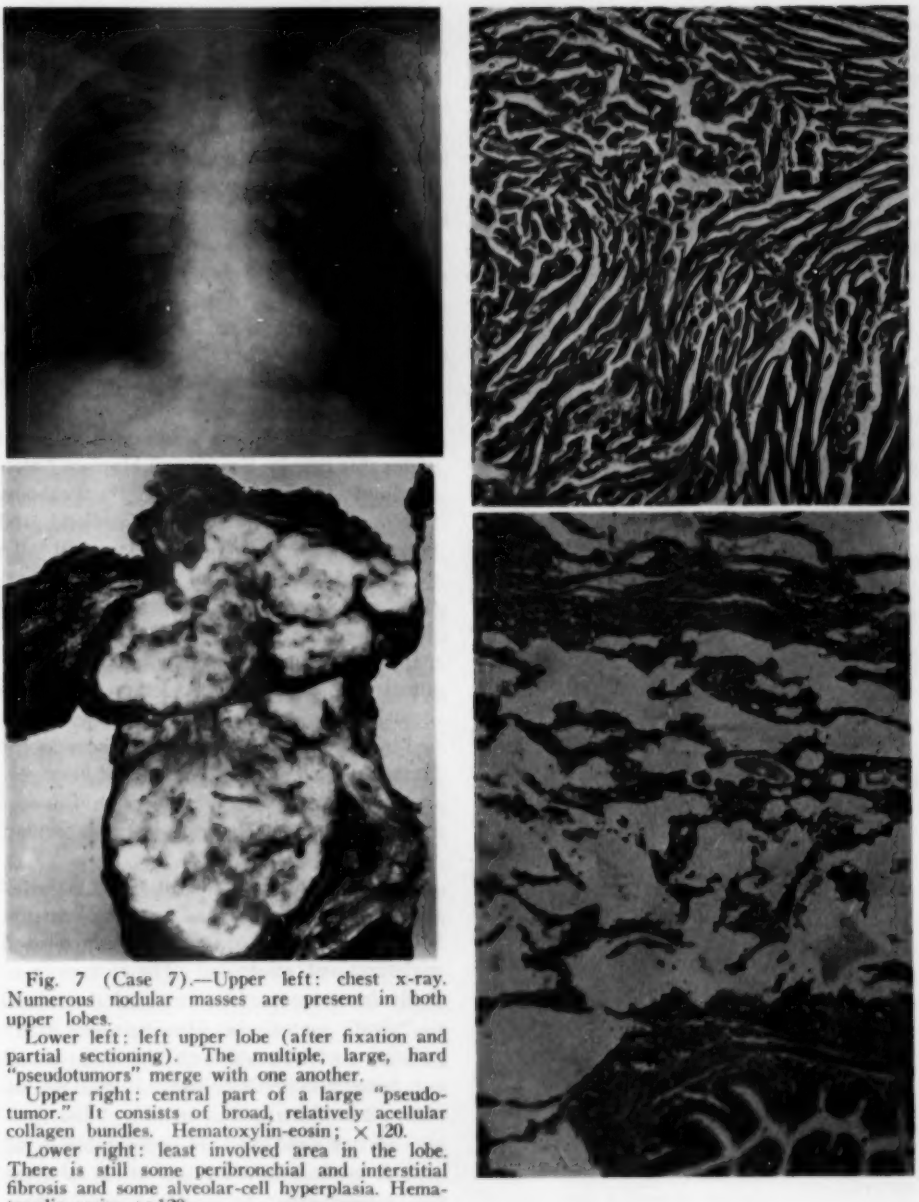


Fig. 7 (Case 7).—Upper left: chest x-ray. Numerous nodular masses are present in both upper lobes.

Lower left: left upper lobe (after fixation and partial sectioning). The multiple, large, hard "pseudotumors" merge with one another.

Upper right: central part of a large "pseudotumor." It consists of broad, relatively acellular collagen bundles. Hematoxylin-eosin; × 120.

Lower right: least involved area in the lobe. There is still some peribronchial and interstitial fibrosis and some alveolar-cell hyperplasia. Hematoxylin-eosin; × 120.

With special stains no organisms were identified.

CASE 7.—This 54-year-old man, an employee of a city street department, had been ill for 18 months. (Careful and extensive inquiry failed to elicit a definite history of pulmonary symptoms prior to that time.) The illness began with precordial discomfort, accentuated by respiration. This was followed by dyspnea and bouts of coughing, both of which increased in severity. The patient was studied by several physicians and in several clinics. A specific diagnosis was not made,

but tuberculosis was considered very improbable. Relatively distinct globular masses of variable size in the upper lobe of both lungs were apparent in roentgenograms. After extensive consultation, the patient was treated with x-rays, 1000 r depth dose.

After admission to this hospital, all diagnostic procedures were again carried out. Roentgenographic findings had changed little (Fig. 7, upper left). Tubercle bacilli were not recovered. A thoracotomy was performed on the left, and the upper lobe was removed. This lobe contained one hard, sharply marginated nodule, 9×6 cm. in size, and several smaller satellite ones (Fig. 7, lower left). These were woody hard.

Microscopically, these lesions consisted centrally of masses of dense, relatively acellular collagen fibers, which were broad and partially hyalinized (Fig. 7, upper right). There were only occasional lymphocytes, plasma cells, and large mononuclear cells. At the margins all infiltration was greater and connective tissue hyperplasia more active. Hyperplasia and anaplasia of bronchiolar epithelium and alveolar lining cells were also present. In lung tissue between the "tumors," septa and alveolar walls were irregularly thickened, due to fibrosis (Fig. 7, lower left), and alveolar lining cells were hyperplastic. The pleura was thickened and fibrotic, and there were emphysematous changes in the distorted lung parenchyma.

These changes at a distance from the pseudotumors are regarded as ample histological evidence that a more generalized disease had at one time involved this lobe. At this late stage of healing, pseudotumors have made their appearance, but the diffuse marks of the previous disease are still apparent. Follow-up examinations have been made and the other "tumors" have not changed appreciably in size. The vital and objective pulmonary capacity of this individual two years after lobectomy, however, is still so limited as to preclude further surgery.

Comment

The histological evidence that these seven cases represent progressive stages of the same disease, manifest by great overlapping in the microscopic appearance, seems acceptable. Cognizant of this variability in severity, Peabody, Buechner, and Anderson[6] divided the Hamman-Rich syndrome into an acute fulminating type (our Case 1), an intermediate type (our Case 2), and a chronic variety (in which the last five cases might be placed, with or without additional subdivisions). Hamman and Rich,[2] in their original description of the condition, which they called acute diffuse interstitial fibrosis of the lungs, anticipated these conclusions to some extent, as did Anderson.[7]

Hamman and Rich[2] referred in some detail to a case not officially included in their group of four which was very similar to, but even more acute than, our Case 1. Other early or acute cases are reported under this title by Beams and Harmos,[8] Potter and Gerber,[9] Schechter,[10] Peabody, Buechner, and Anderson,[6] Kneeland and Smetana (Case 9),[1] and Callahan et al.[4] To the casual observer the extensive hemorrhage in Case 1, which was progressive throughout the patient's illness and the primary factor in his terminal pulmonary insufficiency, may be a deterrent to its inclusion here. Nearly half the cases classified by the original and other authors as the Hamman-Rich syndrome have had hemoptysis of variable severity, however, and in several the microscopic appearance was similar.[2,8,11-13]

Kneeland and Smetana, in 1940,[1] reported the clinical findings in 52 cases of "current bronchopneumonia of unusual character and undetermined etiology." These have generally been accepted as cases of interstitial or "viral" pneumonia. Hamman and Rich[2] pointed out that, although the disease had not been previously observed, the resemblance to influenza was striking. The findings in our first case are comparable in all aspects to those in acute interstitial or atypical pneumonitis, as outlined by Pinkerton,[14] Anderson,[7] Reimann,[15] Golden,[16] and Parker, Jolliffe, and Finland.[13] I am unable to define the line of division between these two conditions.

Case 2 fulfills in all respects the criteria of acute diffuse interstitial fibrosis or pneu-

monitis as reported by the original and subsequent authors. Scarring was severer than in most reported cases but was comparable to that in the cases of Cox and Kohl [17] and Peabody et al.[18] This classification has been accepted also by pathologists at the Armed Forces Institute of Pathology, who stated: "The reviewer has been impressed with the number of examples where known or inferred evidence of viral infection has resulted in lungs with changes similar to these."

It has been observed by many and stated by Clough [19] that the diagnosis of this now-accepted entity is rarely made before examination of the lungs at autopsy. In the vast majority of reported cases this has been true; and perhaps that feature has been accepted by many as a criterion of diagnosis! The patient here reported as Case 3, however, is still living, after three years. Subsequent x-ray films have shown some increase in pulmonary fibrosis and some enlargement of the focal zones. This is almost identical with the progress shown in serial photoroentgenograms reproduced by other authors,[8,9,18,20-22] which also demonstrate the development of greater linear fibrosis, greater nodularity, and often more extensive pleural involvement. The prognosis in Case 3 may be poor; on the other hand, the process has slowed down during the three years since surgery, just as it has in the last four cases.

Case 2 of Schechter,[10] which was of five years' duration, was beginning to show focal zones of scarring. Rubin, Kahn, and Pecker [23] and other authors [6,18] stressed the nodularity which developed. In 10 cases reported by Waddell, Sniffen, and Sweet,[24] the development of focal lesions was reported. It is apparent in their well-illustrated paper that their cases span some latitude of interstitial pneumonitis and that they are comparable at least to our Case 3 and to Cases 6 and 7, with the more "focal" changes.

In Case 4 the pleuritis dominated the clinical picture. Brown and Johnson [25] expressed the belief that the "tumors" of pleura which they reported were inflammatory in origin, and they pointed out their similarity to more diffuse lesions. Their cases indicate that there was continued activity, as seen in our Case 2, as well as in the last three cases. They expressed the belief that identical "tumors" occur in the substance of the lung and postulated that in the past many lesions which were thought to have metastasized to the pleura, the opposite lung, or the lymph nodes were actually multiple focal postinflammatory scars.

In Case 6 the principal lesion was in the parenchyma, but pleura was involved also, with fusion of the lesion to the pericardium and esophagus. This corresponds to the "tumors" reported by Brown and Johnson,[25] which they described as having dense, scar-like collagen and calcification centrally and continuity at the margins with interstitial pneumonitis, with its inevitable scarring and cuboidal hyperplasia of alveolar lining cells. Case 7 reported by Waddell, Sniffen, and Sweet [24] was that of a 12-year-old girl in which the roentgenographic, operative, gross, and microscopic findings were very similar to those in our Case 6.

In the last case (Case 7) any single lesion is simply a large scar, with only mild progressive activity at the margins. The material was also reviewed at the Armed Forces Institute of Pathology, and their comments were in agreement with our opinions. They suggested that the condition may have originated as a pneumonitis of atypical or viral type. It was considered to belong in the group reported from the Institute by Brown and Johnson [25] as postinflammatory "tumors" of the pleura.

These cases compel agreement with Waddell, Sniffen, and Sweet [24] that the duration and severity of symptoms has no clear relation to the extent of the disease or the degree of activity. Rubin, Kahn, and Pecker,[23] speaking of diffuse interstitial fibrosis, recorded the impression that the disease may prove to be not so acutely progressive as had been found in most of the cases reported up to that time. Writing of the same entity, Peabody et al.[18] stated: "We wonder if the

disease is not of its essence a prolonged, chronic affair which remains completely subclinical until the respiratory reserve is finally depleted, at which time symptoms appear and the fulminating portion of the disease runs its course." Certainly, some of these cases are progressing very slowly.

There does seem to be at least some morphologic relation of this condition, particularly as illustrated in Case 2, to pulmonary adenomatosis.[26] The thought that this type of pneumonitis, adenomatosis, and alveolar-cell carcinoma may be related is not a new one. Geever, Neubuerger, and Rutledge[27] described 10 autopsies in which the diagnosis of atypical pneumonia was made. They stated: "Diffuse progressive interstitial pulmonary fibrosis, pulmonary adenomatosis and alveolar-cell tumor of the lung may result from such atypical pulmonary inflammatory reactions." Anderson,[7] like those authors, in a discussion of the pathologic aspects of atypical pneumonias, speculated that the prevalence of that disease might lead not only to an increased incidence of interstitial pulmonary fibrosis but to pulmonary tumors as well, resulting from stimulation of bronchiolar and alveolar lining cells.

Lymphadenopathy has been a prominent finding in the majority of cases reported. When microscopic findings are included, however, only retothelial hyperplasia has been mentioned. Mallory[28] reviewed 6000 consecutive autopsies, in which he found 59 cases of pulmonary fibrosis exclusive of tuberculosis, silicosis, and lipoid pneumonia. Six of these were classified as interstitial fibrosis. In all six cases miliary granulomatous lesions, which he considered typical of Boeck's sarcoid, were present in the lungs. He suggested that his cases be considered localized pulmonary forms of sarcoidosis. I find it difficult to evaluate the remaining lung pathology for comparison with our Case 2 but doubt if they are really similar. I find no other report of sarcoid-like lesions associated with this condition, such as I have seen and recorded in connection with Case 2. The granulomatous and foam-cell reaction recorded by Waddell, Sniffen, and Sweet[24] is clearly not the same thing.

As summarized by Clough,[19] most observers favor a virus as the etiologic agent responsible for this condition. All observers are aware, however, that this suspicion has been substantiated in only a few cases classified as acute interstitial pneumonitis and in none of those clearly resembling the cases of Hamman and Rich. Golden and Tullis[29] suspected that the advanced lesions might be due to failure of resolution and subsequent organization following one or more attacks of acute interstitial pneumonitis.

In a discussion of the viral pneumonias and the pneumonias of probable viral origin, Reimann[15] included psittacosis and stated that at that time (1947) at least 15 pneumonia-producing agents in this group had been isolated from humans, animals, and birds. The pneumonia produced is said by that author to resemble the severest form of the commonly occurring viral pneumonias. In a paper reviewing the pathology of virus pneumonia, McNaught[30] reported six cases of influenza-like bronchopneumonia occurring early in 1940. Three patients died after a brief illness, and two were autopsied. The descriptions and illustrations are of a disease slightly later than that in Case 1. From both his cases a virus antigenically related to psittacosis was found. Two similar cases in that area were cited from which the psittacosis virus was isolated. Many other cases with comparable autopsy findings are discussed, and the author concluded that several viruses were responsible for producing quite similar disease pictures. Parker, Jolliffe, and Finland[13] reported eight autopsies on persons dying of primary atypical pneumonia. Again, the basic findings were consistent with those in our cases, bearing greatest similarity to Case 1. They compared their cases to those of other viral diseases, including psittacosis. Indeed, a high titer of complement-fixing antibodies to psittacosis was demonstrated in one of them.

Reported cases in various stages of this disease, including atypical pneumonia, have appeared in increasing numbers since about 1940. This was followed in a similar way by reports of the more widespread occurrence of psittacosis-like disease in nonpsittacine birds.[31,32] Reports of human infection have appeared in 1948,[33] 1952,[31] and 1954 [34] in increasing numbers. Prolonged infection and a carrier state in humans has been cited.[33,15] Among the nonpsittacine birds, ducks, chickens, pheasants, pigeons and sparrows have been found infected in large numbers. Meyer and Eddie [32] call attention to the steadily increasing numbers of reservoirs and the extension of the host range, indicating that it is the subject of much warranted interest. The similarity of the clinical course and x-ray findings in ornithosis and atypical pneumonia has been stressed by Ward and Birge [31] and others.[35] Wolins [33] has classified his cases under three categories, those of mild nature, those of moderate severity, and those with severe toxic manifestations. Ward and Birge,[31] Ward et al.[34] and Wolins [33] express some concern about cases of this type being numerous and unrecognized.

Summary

The range of diseases described here includes acute interstitial pneumonitis, acute diffuse fibrosing interstitial pneumonitis, chronic and anaplastic pleuritis, and focal "tumors" of the pleura or lung parenchyma or both. Sufficient evidence of the first-named "entity" is apparent in all of them to warrant their inclusion as various manifestations or stages of the same disease process.

Progressive histological characteristics are stressed, and it is pointed out that even in the so-called focal lesions, stigmata of the original, more generalized disease remain, consisting of thickened alveolar walls and nodules of scarring, often with persistent hyperplasia and anaplasia of bronchiolar and alveolar lining cells.

Case 3 demonstrates in excellent fashion the relation which I believe to exist between lungs and pleura in this condition.

Attention is directed to the great hyperplasia and at least near-malignant anaplasia often exhibited. The possible relation to adenomatosis and alveolar-cell carcinoma compels interest.

The pathology in this condition in all its stages is entirely compatible with, and suggestive of, a virus disease. That etiology has been established in some acute cases.

The relative increase in all latitudes of this condition and the parallel increase in time and numbers of ornithosis of birds and man may well be more than coincidental.

Careful attention to investigation of viral etiology in this condition, with special attention directed to the psittacosis-ornithosis group of organisms, seems warranted.

Veterans Administration Hospital.

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Reversible Biliary Cirrhosis in Rat After Partial Ligation of Common Bile Duct

WILLIAM E. JAQUES, M.D., and A. JAMES McADAMS, M.D., New Orleans

Numerous experiments have been performed to produce complete bile duct obstruction in animals.[1-8] These have shown that biliary cirrhosis can be produced by total obstruction of the bile duct. The emphasis in these studies has been on morphogenesis and acceptance of obstruction as the basic mechanism. Our interest in the problem of biliary cirrhosis arose from examination of human surgical and autopsy material. The possibility that biliary cirrhosis due to extrahepatic obstruction might with time be an irreversible phenomenon was suggested by the observations on such material. It seemed reasonable to expect that further encroachment upon the bile ducts by new fibrous tissue would produce more bile stasis, which would, in turn, stimulate further fibrosis. A vicious cycle might thus be established. With this in mind, an experimental procedure was designed in an attempt to answer the following questions:

1. Can partial bile duct obstruction produce biliary cirrhosis?

2. Will biliary cirrhosis produced by this continuous partial common bile duct obstruction regress when the obstruction is relieved?

3. Is infection a necessary factor?

Submitted for publication June 11, 1956.

Presented in part before the American Society for Experimental Pathology, Atlantic City, April 19, 1956.

From the Departments of Pathology, Harvard Medical School and Louisiana State University School of Medicine. Partially supported by the Proctor Fund for the Study of Chronic Diseases, Harvard Medical School.

Material and Methods

Sixty-nine of the Hisaw strain of the original Sprague-Dawley rats were used in this study. The sexes were equally divided. All rats were obtained at approximately 6 weeks of age and weighed about 145 gm. They were maintained on a diet consisting of the Standard Purina Lab Chow. The animals were caged individually according to sex.

Under open ether anesthesia, the skin was prepared and a 2 cm. high midline abdominal incision was made, using sterile precautions, although no bacteriological studies were performed. The common bile duct was isolated and a ligature placed around it as near the liver as feasible. A wire graduated to approximately one-fourth the diameter of the lumen was placed parallel to the bile duct and through the ligature. The ligature was then threaded through a plastic button and tied snugly (Fig. 1). The wire was withdrawn and the operative wound closed. This procedure produced an incomplete common bile duct ligation, which could be released.

The animals were placed into three unequally divided groups. The first group consisted of two controls that were allowed to survive as cage mates

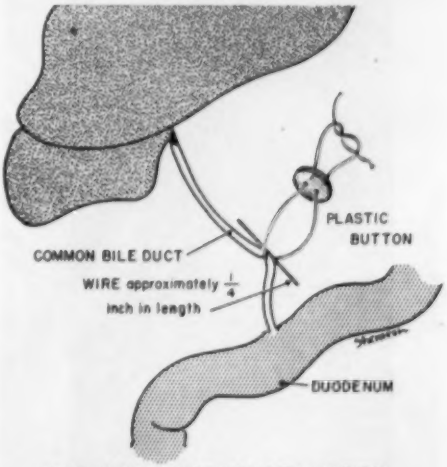


DIAGRAM OF METHOD OF LIGATION

Figure 1

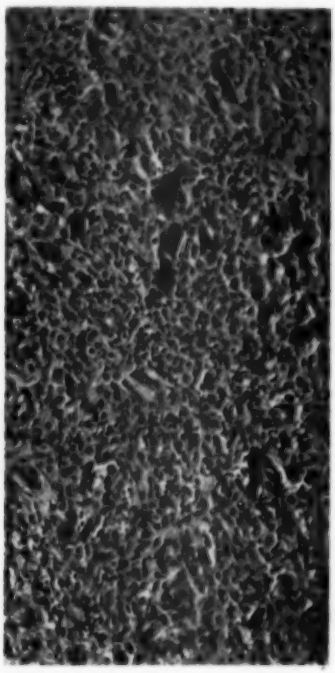
without any surgical procedure. These rats served as a base line of normal hepatic architecture and indicated any endemic disease that might exist.

The second group was composed of 28 rats with an intentional or unintentional complete bile duct ligation. These animals served as a basis of comparison with the partially ligated group. The rats were allowed to survive until they died of biliary cirrhosis.

The third group consisted of 39 rats with partially ligated bile ducts. Six of these animals had their ligations relieved after 15 to 56 days, at which time a liver biopsy was performed. They were allowed to survive an additional 17 to 104 days. Two other animals were explored after 32 and 49 days, at which time a biopsy of the liver was performed. These rats were killed 48 and 59 days after exploration. The remaining 31 animals were killed at daily intervals for the first 10 days, weekly intervals for 6 weeks, and monthly intervals for 4 months.

The animals were killed with ether. The patency of the bile duct was tested at the time the rat was killed by injecting dye into the common bile duct proximal to the obstruction and visualizing the dye as it entered the duodenum. Sections of the liver, spleen, kidneys, adrenals, and common bile duct were fixed in 10% formalin U. S. P. The sections were stained with Bullard's hematoxylin and eosin method.

Fig. 2.—Extreme degree of bile duct proliferation with marked distortion of liver architecture. Complete ligation for two weeks. Hematoxylin and eosin; × 170.



Results

The hepatic alterations with incomplete bile duct obstruction differed considerably from those with complete obstruction. The rats with a complete bile duct ligation had a marked and progressive alteration in the liver. The livers were enlarged and tawny and were friable in consistency. There was a progressive bile duct proliferation, associated with fibrosis and eventual replacement of the majority of the liver cells (Fig. 2). Only one animal with complete ligation of the bile duct survived two months. These findings have been reported previously and will not be expanded on at this time. The rats with an incomplete ligation of the common bile duct showed a significantly different sequence of events and will be described in detail.

Effects of Incomplete Obstruction

The common bile duct was observed to be dilated as early as two days following an incomplete ligation. At seven days there was marked dilatation, up to 1 cm. in external diameter (Fig. 3). The wall was thin, and the duct contained as much as 2 ml. of clear, watery bile. There was a progression of the degree of bile duct dilatation up to three weeks and then a gradual decrease until at four months there was only minimal change.

The liver was frequently, though not invaribly, congested; in the early stages it occasionally had a tawny color and was slightly friable. In rats surviving for four months there were no detectable gross abnormalities in the liver.

First Day.—Rats killed the first day displayed slight bile duct proliferation, especially in the larger portal areas. There was moderate mitotic activity in the bile duct epithelium. Necrosis of liver cells involving single liver cells or groups of two to three cells was found. There was no recognizable

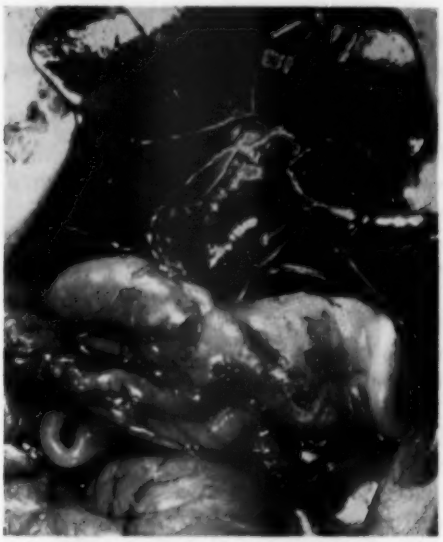


Fig. 3.—Photograph showing marked dilatation of common bile duct at seven days.

increase of mitoses in the liver cells. There was no fibroblastic proliferation.

Second Day.—There was a readily recognizable increase of the changes noted on the first day. Bile duct proliferation was more marked, with numerous mitoses. The necrosis of hepatic cells was more marked and generally periportal in location. An occasional area of wedge-shaped coagulative necrosis was apparent in the periportal portion of liver lobules. An occasional mitosis in liver cells was present. There was only a minimal chronic inflammatory-cell infiltration.

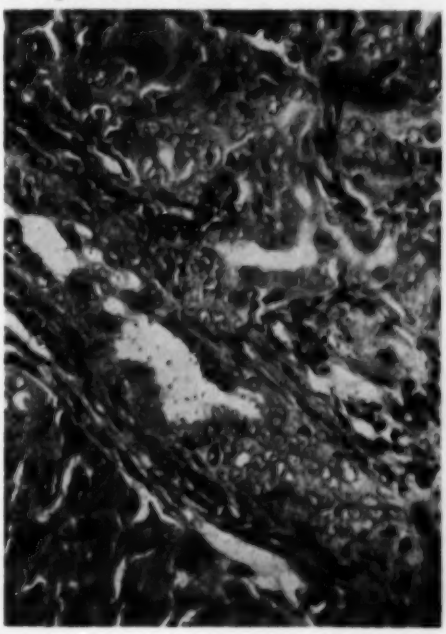
Third Day.—The most characteristic change consisted of an appreciable accentuation of coagulative necrosis of liver cells. The necroses were particularly prevalent subcapsularly. The Kupffer cells persisted in the areas of necrosis. There was early fibroblastic proliferation at the periphery of the necroses, and it would appear that the Kupffer cells assumed a fibroblastic capacity. The bile duct proliferation was more marked, and mitoses in the bile duct epithelium were numerous. No appreciable inflammatory reaction was observed.

Fifth Day.—There was a further increase of bile duct proliferation, with frequent mitoses in bile duct epithelium. The bile duct proliferation often extended from one portal area to another, sharply outlining the liver lobules (Fig. 4). The necroses were decreased, and organization was occurring at the periphery.

Sixth Day.—A still greater increase of bile duct proliferation and circumscribing of the liver lobules was seen. The necrotic zones showed a further increase, with more advanced organization.

Seventh Day.—A still further increase of bile duct proliferation was found, and it was accompanied by a more prominent fibroblastic proliferation. The fibroblastic proliferation was most marked around the adventitia of the portal vein radicles and bile ducts. The zones of coagulative necrosis were still more prominent and were most commonly located about the portal areas. There was moderate mitotic activity in the

Fig. 4.—Bile duct proliferation with slight fibroblastic proliferation. Note extension of bile ducts into periphery of liver lobules. Five days partial ligation. Hematoxylin and eosin; reduced to 84% of mag. × 175.



liver cells, and multinucleated liver cells were noted (Fig. 5).

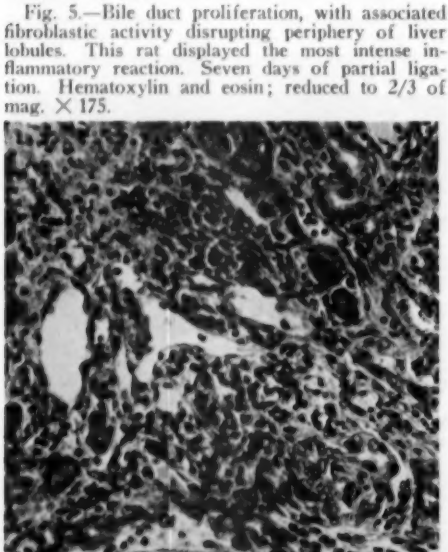
Tenth Day.—There was a pronounced decrease of bile duct proliferation, mitoses in bile duct epithelium, and necrosis of liver cells. The periportal fibrosis was minimal, and hemosiderin pigment was present in the portal areas.

Two Weeks.—The histologic appearance was essentially unchanged from that after 10 days. Only an occasional necrotic liver cell was observed.

Three Weeks.—There were moderate bile duct proliferation and occasional periportal zones of coagulative necrosis. There was moderate periportal fibrosis.

Fourth Week.—A decrease of the degree of bile duct proliferation and of bile duct epithelium mitoses was obvious; no liver-cell necroses were demonstrable. The slight degree of fibrosis persisted, however. There was no appreciable inflammatory reaction, but hemosiderin pigmentation was present in the portal areas.

Fig. 5.—Bile duct proliferation, with associated fibroblastic activity disrupting periphery of liver lobules. This rat displayed the most intense inflammatory reaction. Seven days of partial ligation. Hematoxylin and eosin; reduced to 2/3 of mag. × 175.



Sixth Week.—There was a definite further decrease of the degree of bile duct proliferation. The portal fibrosis showed no appreciable change.

Two Months.—A tendency toward a still further decrease of bile duct proliferation was observed and was associated with a slighter degree of fibrosis.

Third Month.—The bile duct proliferation was minimal, as was the degree of fibrosis.

Fourth Month.—There was a further decrease of bile duct proliferation. One liver had an essentially normal appearance (Fig. 6).

No appreciable difference in the eventual degree of bile duct proliferation and fibrosis could be detected in the third group of rats, either if the bile duct ligation was relieved or if it was allowed to remain.

The kidneys showed no gross changes. Histologically, slight to moderate vacuolar degeneration and varying amounts of bile pigment in the tubular epithelium were noted.

The spleen and adrenals were normal.

Comment

It was immediately apparent that there was a marked difference in the hepatic changes following complete and incomplete bile duct ligation. Numerous studies have correlated the sequence of events in the liver following complete bile duct ligation.[1-5] Cameron and Oakley[1] demonstrated the course of chronologic development in the rat. Koch-Weser et al.[2] showed the influence of the site of ligation on the hepatic changes.

The hepatic changes following complete high common bile duct ligation correlated closely with those of Cameron and Oakley.[1] The rats with incomplete bile duct ligation, however, showed an immediate development of bile duct proliferation, which reached a peak around the third week. After this time there was an appreciable decrease of the bile duct proliferation and fibrosis. Indeed, at four months, it was difficult to distinguish the liver from that of normal rats.

This reversibility is also suggested by a human case report in which, following re-

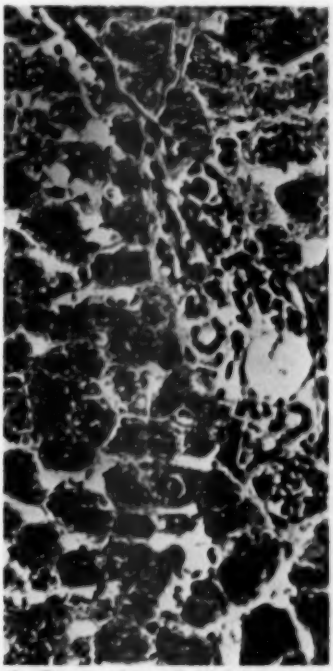


Fig. 6.—Return of portal triads to an essentially normal appearance. Four months of partial ligation. Hematoxylin and eosin: × 175.

lief of obstruction, serial liver function studies, over a 30-month period, showed marked improvement.[9] The data of other investigators also suggest the possibility that the process of biliary cirrhosis regresses when the obstruction is relieved.[1,5]

The reason for the differences in the hepatic response in the rats with complete and incomplete bile duct ligation are not so apparent. It seems reasonable to assume that, in the early stages of an incomplete ligation, there is probably an associated edema at the site of ligation from surgical trauma. This would produce a complete obstruction initially. Certainly, the finding of complete obstruction in those animals killed early, and in which an incomplete ligation was attempted, would substantiate this. Likewise, with time, the marked decrease of the size of the bile ducts following an incomplete ligation also is in favor of this hypothesis.

The reasons that partial bile duct ligation would produce the described sequential events remain obscure. There are adherents of a simple cholestatic mechanism[3,4,8] and other adherents of a cholangitic factor.[1,10] Our data gave no evidence of an important cholangitic component. The fact that rats are resistant to infection made a cholestatic factor more reasonable.

Summary

A method for the production of subtotal biliary obstruction is described. With this method, previous observations on the transient nature of "obstructive biliary cirrhosis" have been confirmed and extended.

During prolonged incomplete obstruction of the proximal portion of the common bile duct, biliary cirrhosis usually regresses spontaneously. This regression occurs whether or not the partial ligation is intentionally relieved.

Department of Pathology, Louisiana State University School of Medicine.

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Electrolyte Imbalance and Intracellular Potassium-Sodium Exchange

M. H. RAHMAN, M.D.; L. E. FRAZIER, M.S.; R. H. HUGHES, and P. R. CANNON, M.D., Chicago

It is generally believed, mainly on the basis of studies of electrolyte exchange in muscle, that when potassium ions diffuse out of the cell, sodium ions enter and replace them. The latter ions, in turn, tend to be removed from the cell by a complicated mechanism termed the "sodium pump." If, however, the homeostatic mechanisms which control the usual functioning of the sodium pump fail to effect adequate extrusion of sodium ions, intracellular alterations may ensue. It has also been suggested that even under essentially normal intracellular conditions, sodium ions, if present in increased concentrations in the interstitial fluid, may also enter the cell and displace potassium. If this occurs, as, for example, in such conditions as congestive heart failure, renal failure, toxemia of pregnancy, and eclampsia, or because of excessive action of adrenal mineralocorticoids, or following injections of desoxycorticosterone acetate, it is possible that an intracellular accumulation of sodium ions may cause a sufficient extrusion of potassium ions to produce cellular damage, especially in cardiac or respiratory muscle. Indicative of this possibility is the evidence that sodium ions, probably in conjunction with hydrogen ions, can enter cells depleted of potassium and exert a toxic effect.[1]

The following experiments were undertaken in an effort to determine whether the consumption by young rats of diets nutritionally adequate, but containing salt mixtures high in sodium and low in potassium, can induce lesions characteristic of potassium deficiency, particularly focal necroses of the myocardium. The appearance of these lesions under such circumstances would suggest the possibility of potassium displacement from muscle cells as a result of intracellular ionic imbalance. It was also hoped to investigate further the problem of renal injury and hypertension, in view of the reports by Meneely, Tucker, Auerbach, and Darby of the development of such abnormalities following the feeding to growing rats of rations containing unusually large quantities of sodium chloride.[2,3]

Submitted for publication Sept. 28, 1956.

The Department of Pathology, The University of Chicago, the School of Medicine.

This work was done in cooperation with the U. S. Navy, Office of Naval Research. The Douglas Smith Foundation for Medical Research of the University of Chicago also cooperated.

Experimental Procedures

Young male albino rats (Sprague-Dawley strain), weighing between 102 and 110 gm., were used. They were kept in steel wire cages, 5 to 10 animals to a cage, and were fed a basal ration adequate in protein, vitamins, and calories but containing varying amounts of sodium chloride and almost minimal daily allowances of potassium salt. The 46 rats were divided into five groups, as indicated in Table 1.

It should be noted that only the rats in Group 4 received amounts of sodium chloride approaching the higher levels used by Meneely and associates and that the severest lesions observed by them tended to occur in animals eating rations containing from 8.4% to 9.8% of sodium chloride. Moreover, their animals were fed ad libitum with unrestricted potassium intakes, whereas in our experiments the dietary intakes were limited in order to insure a constancy of intake of both sodium and potassium. Thus it is evident that the objectives and the experimental procedures differed appreciably in the two groups of experiments. The ra-

TABLE 1.—*Groups of Rats on Basis of Potassium and Sodium Intakes*

Daily Intakes of Potassium and Sodium Chloride per Rat, Mg.	No. of Rats	1-34 Wk.		35-53 Wk.	
		KCl	NaCl	KCl	NaCl
Group 1: Potassium and sodium intakes "normal"	6	188	46	188	46
Group 2: Potassium and sodium intakes "low"	10	20	20	20	20
Group 3: Potassium intake "low," sodium intake "high"	10	20	500	20	1,000
Group 4: Potassium intake "low," sodium intake "highest"	10	20	750	20	1,500
Group 5: Potassium intake "normal," sodium intake "high"	10	188	500	188	1,000

tions were prepared by adding the requisite amounts of sodium chloride and potassium chloride to the basal ration* devoid of these compounds and were fed initially in amounts of 10 gm. daily. This gave a value of approximately 3.8 Cal. per gram. After the 34th week the daily amount of ration offered was raised to 14 gm. by the addition of dextrin and water, allowing a daily caloric intake of 53 Cal. At the same time, for reasons to be mentioned shortly, the daily offering of sodium chloride was doubled for the rats in Groups 3, 4, and 5.

Through the 53 weeks of the experiment weights of the rats were recorded weekly. Food consumption was excellent except in the animals of Group 4, in which, during the last five weeks, the food intake averaged about 4 gm. a day less than that in the other groups. All the animals gained weight, the largest gains occurring in the animals of Group 1 and the smallest in those of Group 4. The animals in general remained healthy with the exception of three in Group 3, which showed evidences of respiratory difficulty between the 32nd and the 40th week and were accordingly isolated. One died, but the other two recovered and were put back into the group cage on the 40th week. Only one rat in Group 4 died, in the 53d week. Necropsy disclosed acute pulmonary edema and the presence of areas of focal myocardial necrosis, indicative of potassium deficiency. At no time were there any evidences of generalized edema.

Because of the possible development of hypertension, as reported by Meneely, Tucker, Darby, and Auerbach, blood pressure measurements were taken after nine months in the rats of each group and twice a month thereafter until the 53d week, using a photoelectric method.[4] No elevations of blood pressure were detected. Blood pressures were again taken at the time of killing of the animals at the 49th, 52d and 53d weeks, by direct introduction of the blood pressure needle into the abdominal aorta under light ether anesthesia. Again, no elevations of blood pressure were found.

An animal from each group was killed at intervals (6th, 16th, 33d, and 42d weeks); the tissues were fixed in 10% solution of formaldehyde and embedded in paraffin. Sections stained with hematoxylin and eosin were prepared from the heart, kidney, liver, adrenals, pancreas, spleen, lungs, and striated muscle. Fat stains with Sudan III were also made on frozen sections of the liver, kidneys, heart, and adrenals. All sections were essentially normal. It was decided, therefore, at the 35th week, to double the intakes of sodium chloride in the animals of Groups 3, 4, and 5. No further animals were killed until the 47th, 49th, 52d, and 53d weeks. On the 53d week all remaining rats were killed and tissues were taken as before.

* Composition of basal ration: fibrin, 15%; dextrin, 42.5%; corn oil, 16%; cellulose, 7.5%; percomorph liver oil, 0.8 drop per 100 gm.; vitamin mixture, 1.5%; Hawk and Oser salt mixture, in which sodium and potassium salts are replaced by the equivalent magnesium compounds, 6.29%; water added to make 100 gm. Composition of vitamin mixture: nicotinamide, 0.4%; calcium pantothenate, 0.2%; pyridoxine HCl, 0.1%; riboflavin, 0.2%; thiamine HCl, 0.1%; sucrose, 99.0%.

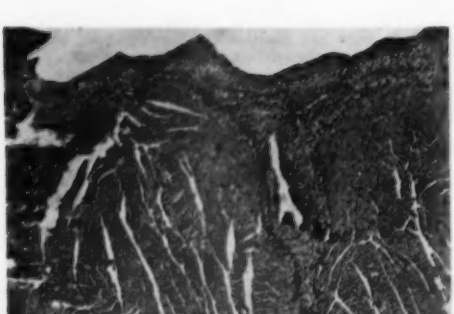
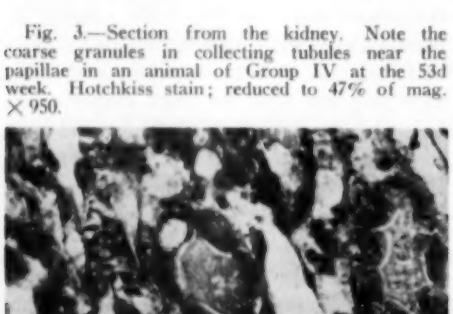


Fig. 1.—Section from the myocardium demonstrating an extensive subendocardial lesion in an animal of Group IV at the 53d week. Hematoxylin and eosin; reduced to 47% of mag. × 65.

Microscopic lesions indicative of potassium deficiency were first seen in the animals of Group 4 (highest salt group) killed at the 47th week. These lesions are shown in Figures 1 and 2 and are characteristic of potassium deficiency. By the 53d week they were present in the hearts of each rat of Group 4 but not in the hearts of any of the animals in the other groups.

A further indication of potassium deficiency was the finding, particularly in the animals of Group 4 and to a less extent in the rats of Groups 3 and 5, of renal lesions resembling those described by Spargo.[5] These appeared as a distention and dilatation of the proximal and distal convoluted tubules, with some proliferation of epithelial cells and a tendency to multilayering. Hotchkiss stains revealed the presence of coarse intracellular granules in the tubules near the papillae in rats killed in the 52d week (Fig. 3). No arterial changes were observed nor any significant changes in the adrenals.

Fig. 3.—Section from the kidney. Note the coarse granules in collecting tubules near the papillae in an animal of Group IV at the 53d week. Hotchkiss stain; reduced to 47% of mag. × 950.



Because of this morphological evidence of potassium deficiency in association with a high dietary intake of sodium chloride, additional experiments were performed in which potassium balances were determined over a period of 10 weeks in a second series of young rats fed identical low-potassium diets, but in one group with the sodium chloride content high, and in the other group, low. There were six rats in each group. The experiments were designed with the assumption that, if potassium excretion should be higher in the animals eating the high-salt ration, this might indicate a displacement of intracellular potassium ions by sodium ions. A limitation of growth would be further evidence of a loss of potassium. Initially each 10 gm. of ration contained 20 mg. of potassium chloride and approximately 1000 mg. of sodium chloride. The amount of ration was gradually increased from week to week so that after five weeks each animal received 13 gm. of ration daily, thus providing adequate caloric intakes in relation to increasing size.

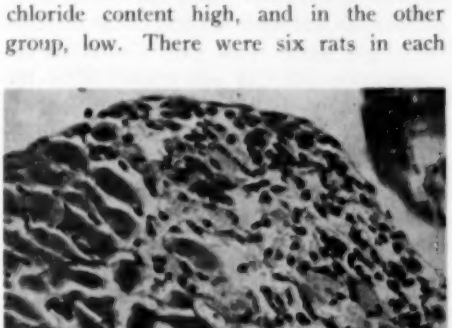


Fig. 2.—Section from the myocardium demonstrating an early focal lesion in an animal of Group IV at the 47th week. Hematoxylin and eosin; reduced to 47% of mag. × 500.

Urines and feces were collected and

TABLE 2.—*Potassium Balances, in Microequivalents, in Rats Fed High-Salt and Low-Salt Rations*

Week	1	2	3	4	5	6	7	8	9	10	Total, mEq
High-salt	−100	620	410	583	763	677	813	883	767	650	+ 6.07±0.32
Low-salt	640	910	833	900	1165	1080	1203	1207	1028	967	+10.02±0.29

pooled weekly and determinations of potassium excretion made by means of a flame photometer. The results are shown in Table 2, where it is seen that the losses of potassium were consistently higher in the animals eating the high-salt ration. Expressed differently, potassium retention was less, approximately in the ratio of 6:10. The animals eating the high-salt ration also gained less weight, averaging 131±5.6 gm. per rat, in comparison with 153±1.3 gm. for those eating the low-salt ration.

At the end of the 10th week all animals were killed for carcass analysis. The findings are shown in Table 3. Comparison of the analytical results with determinations made on control animals killed at the beginning of the experiment made possible the estimation of the extent of change in carcass components in relation to the experimental procedures. Although the rats eating the high-salt ration retained more sodium and less potassium than did those on the low-salt ration, they gained less weight and less water, thus substantiating the lack of any visible evidence of edema.

Despite this evidence that the tissues of the rats eating the high-salt diets retained more sodium and less potassium than did those of the animals eating the low-salt diet, the question remained whether the loss of potassium was attributable to cellular displacement by sodium, or whether it was a result of diuresis. In the latter event the possibility would remain that sodium in the interstitial fluid may merely have replaced potassium lost from the cells. Arguing against this possibility are the observations of Seldin and Tarail [6] that, in human subjects in whom diuresis was induced by the ingestion of large quantities of water or the administration of solutions of dextrose or mannitol, no evidence was found of an increased excretion of urinary potassium during the periods of diuresis.

In an attempt to clarify the question further, seven young rats were fed basal diets containing identical amounts of potassium (20 mg. per day) but with either high-sodium or low-sodium content. Concomitantly, the amino acid and fluid intakes were equalized by supplying the animals with a potassium-poor solution of fibrin hydrolysate (Aminosol) so diluted as to compel the animals to drink considerable amounts daily in order to satisfy their amino acid needs. Potassium balances, accomplished over a period of five weeks, revealed a definitely lowered retention of potassium in the animals on the high-salt intake, indicating that

TABLE 3.—*Data from Carcass Analyses (Average) of Rats Fed High-Salt and Low-Salt Rations*

	No. of Rats	Water, Gm.	Fat, Gm.	Protein, Gm.	Ash, Gm.	Total, Gm.	Na, mEq.	K, mEq.
Controls	3	71.3 ±5.2	7.6 ±0.5	18.1 ±2.2	3.3 ±0.35	100.3	4.67 ±0.54	7.05 ±0.93
High-salt	6	145.7 ±4.8	23.2 ±0.95	45.7 ±2.4	7.65 ±0.42	222.25	13.99 ±1.2	14.3 ±0.65
Low-salt	5	159.7 ±2.34	30.3 ±3.5	49.7 ±1.26	8.14 ±0.17	247.84	12.59 ±0.84	16.21 ±0.5
High-salt, change		74.4	15.6	27.6	4.35	121.9	9.32	7.25
Low-salt, change		88.4	22.7	31.6	4.84	147.54	7.92	9.16

the loss of potassium in the urine was not the result of high fluid intake alone. During the experiments the amino acid solution was diluted from day to day until each animal was drinking nearly 60 ml. daily. The average daily fluid intake per rat for the five weeks was approximately 53 ml. for the three high-salt rats and 55 ml. for the four low-salt animals. The weight gains of the former averaged 44 gm., or approximately 9 gm. per week. For the low-salt rats the average weight gain was 82 gm. per rat, or approximately 16 gm. per week. With reference to potassium balances, the average for the entire period for the high-salt animals was $+250\mu$Eq, whereas for the low-salt rats it was a $+4814\mu$Eq.

Of particular interest was the finding, at the end of the experiment, of myocardial necroses characteristic of potassium deficiency in all the animals on the high-salt intake and none, or only minimal lesions, in those on the low-salt intake. Inasmuch as the potassium and fluid intakes were essentially identical throughout, this production of potassium deficiency in relation to a high-salt intake cannot be attributed to diuresis; on the contrary, it adds further weight to the probability that the diet actually led to the displacement of potassium from myocardial fibers.

Comment

These experiments afford further evidence that an imbalance between sodium and potassium ions in growing rats can lead to the development of potassium deficiency, as indicated both by the appearance of focal necrosis of cardiac muscle and by a greater excretion of urinary potassium. They furnish evidence, also, as to some of the mechanisms concerned. The ionic interrelationships affected are presumably controlled by homeostatic mechanisms, which undergo certain alterations as the ionic imbalances occur. The increased extracellular concentration of sodium ions may favor the cellular entrance of these ions beyond the capacity of the sodium pump to remove them, and, as a result, displacement of potassium ions ensues. Another possibility is that sodium ions may competitively hinder the entrance of potassium ions into cells. Such a possibility might be regarded as an instance of "ionic interference."

Fenn [7] emphasized the point that, since sodium ions continuously diffuse into cells, the sodium pump must function continuously. If the action of the pump diminishes, the intracellular concentration of sodium increases and that of potassium lessens. Fenn also remarked that, despite the meager amount of information relative to the action of the sodium pump, its action is unquestionably active; and he predicted that in time pathological conditions will be found resulting either from hyperactivity or from hypoactivity of this pump as a sodium-transporting mechanism.

The failure of the animals in these experiments to develop hypertension or severe renal lesions, even after 53 weeks, is of interest in relation to the experiments of Meneely and his associates. This failure may be attributable to too little sodium chloride in the diet or possibly to the low-potassium intake. In view of the fact, however, that potassium-deficient rats can be protected against the development of myocardial necrosis by the feeding of a low-salt diet, it is possible that renal lesions related to the development of hypertension may also be less likely to develop in relation to high-sodium intakes when accompanied by minimal intakes of potassium. Our experiments merely suggest the possibility but do not supply an answer to the question.

Summary

The feeding to growing rats of nutritionally adequate diets high in sodium chloride content but low in potassium led to markedly increased urinary excretion of potassium and the development of focal myocardial necroses characteristic of potassium deficiency. Such lesions did not appear, or were min-

imal, in animals fed similar diets low in sodium chloride.

These experiments support the point of view that ionic imbalances between sodium and potassium, under conditions of excessive intakes of sodium, may lead to an intracellular displacement of potassium and a subsequent development of cardiac lesions indicative of potassium deficiency. The inference is that a preponderance of sodium ions within the cell may be the determinant of potassium displacement.

Department of Pathology, University of Chicago.

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A New Method of Dissection of the Heart

FELIX L. RODRIGUEZ, M.D., and LEOPOLD REINER, M.D., New York

In accordance with general principles of autopsy technique, the dissection of the heart aims at maximum exposure with a minimum of incisions. Emphasis on one or the other anatomic feature of the heart characterizes extant methods of dissection. A widely used modification [1] of Virchow's method [2] employs four longitudinal incisions which, figuratively speaking, trace the route of the blood in and out of the cardiac chambers (Fig. 1 *I*). Each ventricle is opened in two planes, one being anterior, alongside the interventricular septum, and the other lateral, through the margo obtusus and margo acutus, respectively. In Zenker's method [3] an anterior transverse cut serves as a base line for four longitudinal incisions which are similar to those of Virchow (Fig. 1 *II*). A method reported by Sikl [4] consists simply of serial transverse sections through the ventricles (Fig. 1 *III*). In Schlesinger's method [5] one extirpates the interventricular septum and unrolls the cardiac cone (Fig. 1 *IV*) to allow angiography of the coronary system in one plane.

The method to be described combines in modified form certain elements of the methods of Virchow and Schlesinger. It shares in the advantages of both and is simpler than either. Only two planes of incision are employed, one to either side of the cardiac septa. Exposure is maximal. The preservation of topographic relationships and the ease of subsequent reconstruction compare favorably with those obtained by other methods. Although described for the extirpated heart, the same incisions may be used with the heart in situ.

Submitted for publication Aug. 3, 1956.

From the Departments of Pathology, Beth Israel Hospital and Harvard Medical School, Boston, and the Departments of Pathology, the Bronx Hospital and Albert Einstein College of Medicine, New York.

Supported in part by a research grant (H-2542) from the National Heart Institute, National Institutes of Health, U. S. Public Health Service, and in part by a grant from the American Heart Association and the Lebanon County (Pa.) Heart Association.

Method

The first incision transects the pulmonic valve and is continued down to the apex so as to separate the anterior wall of the right ventricle from its attachment to the interventricular septum (Fig. 2 *A* and *B*). This incision is identical with Virchow's Step II and Schlesinger's Step I. The moderator band is transected close to its septal insertion.

The second incision starts at the ostium of the superior vena cava and divides the right atrium along its anterior attachment to the interatrial septum. It is continued in the same plane through the tricuspid valve, the crista supraventricularis, and, for the second time, the pulmonic valve (Fig. 2 *B* and *C*).

The third incision divides the posterior wall of the left atrium between the ostia of the right superior and right inferior pulmonary veins. It is carried through the mitral valve into the left ventricle down to the apex, alongside the posterior attachment of the interventricular septum (Fig. 2 *D* and *E*). It is advisable to divide the posterior papillary muscle at its base.

The fourth incision (optional) opens the aortic valve along a plane which circumvents the previously divided mitral valve. It separates the lateral segment of the aortic ring and the medial segment of the mitral ring from the base of the interventricular septum posteriorly (Fig. 2 *E* and *F*).

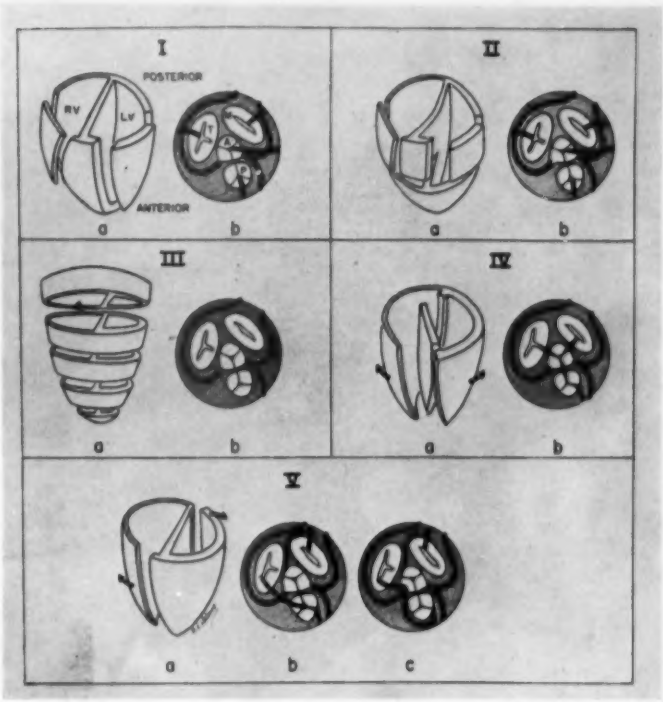

Fig. 1.—Diagrams of various extant methods for the dissection of the heart. *I*, modified Virchow's method; *II*, Zenker's method; *III*, method published by Sikl; *IV*, Schlesinger's method; *V*, method described in text. In each box the anterior view of the ventricles is shown in *a* and the base with the valves and (hatched) coronary arteries in *b*. The respective incisions through the valves are indicated by heavy, solid lines. The broken lines in *V b* and *V c* represent the (optional) fourth incision of the method described in text. The variant incisions of the present technique are illustrated in *V c*. Arrows in *IV* and *V* indicate the directions in which the ventricles are "unrolled." Abbreviations: *LV*, left ventricle; *RV*, right ventricle; *A*, aortic valve; *P*, pulmonic valve; *M*, mitral valve; *T*, tricuspid valve.

The following variant incisions (Fig. 1 *V c*) are useful on occasion: (*a*) To avoid cutting the pulmonic valve twice, the second incision is carried into the ventral part of the conus arteriosus and is made to join the first incision below the pulmonic ring. (*b*) The right coronary artery, which is transected near its ostium by the second incision, may be preserved in continuity by cutting out a button of aortic wall about its coronary ostium and by incorporating in the incision the piece so isolated.

Comment

In the method presented here, each ventricle is incised once, instead of twice, as in Virchow's method (Fig. 1 *I* and *V*). This is made possible by opening each atrium along the same plane of incision as that employed for the corresponding ventricle. Without compromising full exposure, the preservation of topographic relationships is thereby improved and reconstruction is simplified (Fig. 2*G*). Two considerations were important in our preference to open the right side of the heart anteriorly and the left side posteriorly rather than vice versa: the free accessibility of the pulmonic valve from the anterior aspect, and the greater frequency of pathological changes in the aortic than in the pulmonic valve.

The method shares with Schlesinger's the principle of "unrolling" (Fig. 1 *IV* and *V*). However, the interventricular septum is not extirpated; the aortic valve is divided once (if at all), instead of twice, and the left and right cardiac chambers are unrolled in the same instead of in opposite directions. The endocardial surface of one-half the heart and the epicardial surface of the other present on each side of the unrolled specimen (Fig. 2*F*). The coronary arterial tree can be laid out in one plane, with its branches to the interventricular septum intact (Fig. 3). The resulting display of the coronary arteries appears more satisfactory than the classic diagram of Spalteholz,[6]

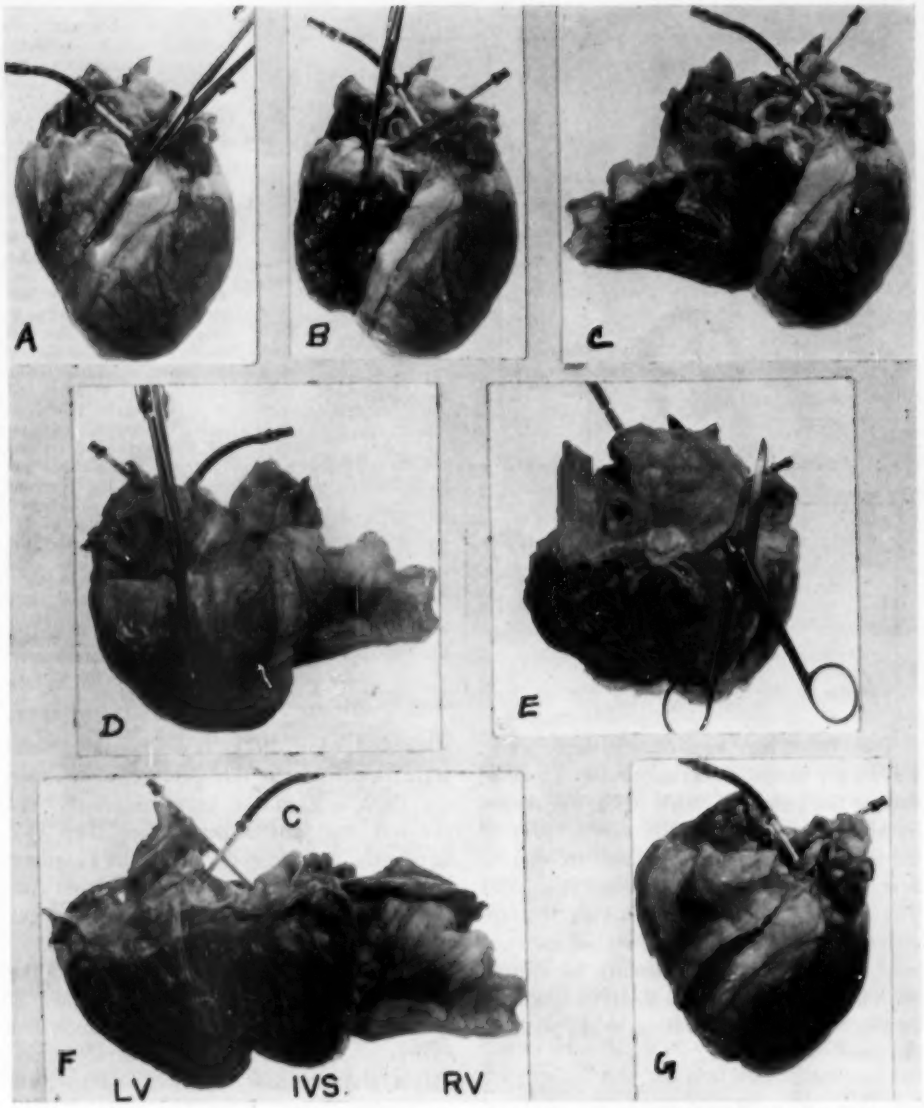

Fig. 2.—Photographs of the various steps of the dissection procedure described in text. *LV*, left ventricle; *IVS*, interventricular septum; *RV*, right ventricle; *C*, cannula.

which represents the vessels to the interventricular septum incompletely, or the coronary angiogram of Schlesinger,[5] which separates these vessels from the rest of the coronary system.

Summary

A new method for the dissection of the heart is described which employs only two planes of incision, one to either side of the cardiac septa. Because it is an "unrolling" procedure, the coronary arteries can be visualized angiographically in one plane, the branches to the interventricular septum remaining in continuity with the parent vessels. The technique affords full anatomic exposure, yet preserves topographic re-

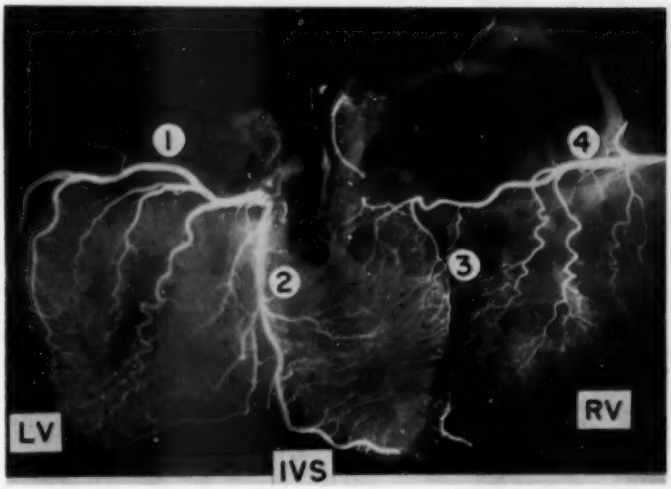

Fig. 3.—Coronary angiogram of a heart injected with Schlesinger's mass[7] and dissected by the method described in text. *LV*, left ventricle; *IVS*, interventricular septum; *R*, right ventricle; (*1*) left circumflex artery; (*2*) left anterior descending artery; (*3*) right posterior descending artery; (*4*) right coronary artery.

lationships well. Reconstruction of the dissected heart is simple.

Beth Israel Hospital (3) (Dr. Rodriguez).
The Bronx Hospital (56) (Dr. Reiner).

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Esterase Activity of Developing Bones and Teeth

M. S. BURSTONE, Bethesda, Md.

Although several enzyme systems have been associated with the development and calcification of bone, a recent review has indicated that bone matrix "per se" does not exhibit enzyme phosphatase activity.[1] There are, however, references in the literature to the presence of alkaline phosphatase in developing bone matrix.[2,3]

In the present work a series of procedures were employed for the histochemical demonstration of esterase in the matrices of developing bones and teeth. In addition, two methods for the demonstration of alkaline phosphatase were used in an attempt to verify the findings of other studies.

Methods

The heads and knee joints of 2-, 5- and 8-day-old mice were frozen and dried, then infiltrated with and embedded in paraffin (U. S. P., m. p. 54-56 C).[4] Six animals from two different litters were used in each age group. In addition, two 5-day-old hamster heads were studied. The undecalcified tissues were sectioned at 6μ, dry-mounted on albumenized slides, deparaffinized with petroleum benzin N. F. (petroleum ether), followed by acetone and water, and then placed in the substrate solution.

A series of esters derived from 1- and 2-naphthols, and also 2-oxy-naphtholic acid anilide (naphthol AS) were used. These included 1-naphthyl acetate, 1-naphthyl propionate, 6-bromo-2-naphthyl acetate* and the naphthol AS acetate of Gomori.[5] In addition, several new substrates were synthesized from naphthols of the AS series†[6] by a modification of the Schotten-Baumann procedure, using 1.5 times the calculated amount of sodium hydroxide and an excess of the acid anhydride in tetrahydrofuran or acetone. The esters were recrystallized from cold methanol or methanol-water, after which the following analytical data were obtained:

(*a*) Naphthol AS-D acetate
Analysis: calcd. C 75.2%, H 5.3%, N 4.4%
found C 75.0%, H 5.5%, N 4.3%
m. p. 165 C

(*b*) Naphthol AS-OL acetate
Analysis: calcd. C 71.8,% H 5.1%, N 4.1%
found C 72.1%, H 4.0%, N 4.0%
m. p. 128 C

(*c*) Naphthol AS-D chloroacetate
Analysis: calcd. C 67.8%, H 4.5%, N 3.9%, Cl 10.02%
found C 67.3%, H 4.5%, N 4.5%, Cl 10.61%
m. p. 162 C

(*d*) Naphthol AS-RT acetate
Analysis: calcd. C 75.2%, H 5.3%, N 4.4%
found C 75.0%, H 5.5%, N 4.3%
m. p. 147 C

(*e*) Naphthol AS-MX acetate
Analysis: calcd. C 75.7%, H 5.75%, N 4.2%
found C 75.3%, H 5.94%, N 4.2%
m. p. 112 C

The AS-D and AS-OL acetates appear to be the counterpart of the British AS-OT and AS-FR acetates described by Pearse.[7] However, no analytical data were given in his report.

With the 1- and 2-naphthol esters the substrate solutions were adjusted to a pH of 7.5, while with the AS esters a pH of 7.1 (0.2 M tris buffer) was used. Coupling was accomplished with diazotized *p*-chloro-*o*-anisidine or *o*-aminoazotoluene.‡ Sections were incubated for one hour at room temperature. All substrates were first dissolved in 1 ml. of N,N-dimethylformamide, followed by distilled water and buffer.

Some sections (dry) were heated to about 110 C for four minutes prior to incubation, while others were incubated in solutions which contained diazonium salt but no substrate. Sections were also immersed in solutions of naphthol AS-D and then transferred to the diazonium salt solution. Some sections were first treated with diazonium salt followed by the naphthol. In addition, sec-

Submitted for publication June 13, 1956.

National Institute of Dental Research, National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare.

* Dajac Laboratories, Inc., Leominster, Mass.

† Naphthols furnished through the courtesy of the Pfister Chemical Works, Inc., Ridgefield, N. J.

‡ General Dyestuffs Corporation, Sales Division of General Aniline & Film Corporation, New York.

tions were immersed in a dye prepared by coupling naphthol AS-D with diazotized aminoazotoluene. None of the sections thus treated showed any genuine staining reaction. In fact, it was impossible to stain bone matrix by any of the above-mentioned procedures. In some sections a pale color was visible in some soft-tissue areas. It would appear that frozen-dried deparaffinized tissues do not have affinity for naphthols of this type used unless it is released enzymatically on a submicroscopic level and then coupled in situ. Sections were also incubated at a nonoptimal pH (8.5), at which the naphthol ester will decompose spontaneously. No staining of bone was visible after an hour's incubation. Some stained sections were washed with acetone to remove the dye and then reincubated for one hour. In this case no staining resulted.

The esterase reactions were also studied by the interposition of certain potential esterase inhibitors prior to or during the hydrolysis period. These included the following:

Sodium arsanilate	0.002 M
Sodium fluoride	0.003 M
Physostigmine salicylate	10^{-4} M
Benzethonium (Phemerol) chloride	1:1000
Benzalkonium (Zephiran) chloride	1:1000 §
Isoflurophate (diisopropyl fluorophosphate; DFP)	10^{-4} M §
Diethyl-*p*-nitrophenyl phosphate (E-600)	10^{-4} M §
di(2-chloroethyl) methylamine HCl (DDM)	10^{-4} M §

All inhibitor studies were carried out in conjunction with the AS-D acetate. In addition, a postcoupling procedure was also used in an attempt to verify the findings. Sections were immersed in the substrate and buffer alone for one hour and then transferred to the diazonium salt solution. Sections so treated showed staining of mucous glands (nasal epithelium) and end-plates (tongue), as well as bone and tooth matrices. Some sections were also treated with isoflurophate and E-600 for one hour, followed by the postcoupling method. Controls for all pretreated sections were immersed in distilled water or saline.

Two methods for alkaline phosphatase, the calcium-cobalt procedure and the sodium 1-naphthyl phosphate method,[5] were used. Incubation times ranged from two to three hours.

§ Sections pretreated with potential inhibitor for one hour prior to incubation. All other inhibitors were incorporated in the substrate mixture. The effect of metals was studied by the incorporation of 0.001 M concentrations of Cu SO_4, Cd SO_4, or Cd $(SO_4)_3$ in the substrate mixture.

Fig. 1.—Knee joint of 5-day-old mouse showing esterase activity in developing bone (naphthol AS-D acetate). Nuclei stained with hematoxylin. Reduced to 8/9 of mag. × 160.

Observations

Esterase.—Esterase activity was observed in both intracartilaginous and intramembranous bone formation (Fig. 1). Reactive areas stained an intense shade of red. In the younger animals (2 and 5 days old) the bone matrix for the most part stained homogeneously. However, where calcification had taken place only the outer border of uncalcified matrix reacted. This picture was particularly noticeable in the 8-day-old mice. Calcifying cartilage stained intensely, with the strongest reaction present adjacent to the hypertrophic zone of cartilage cells. The staining reaction of bone matrix of 5-day-old animals with the various substrates is summarized in the accompanying Table.

Activity was also observed in both dentin and enamel matrices of the unerupted molar teeth. The zone of predentin did not react, while the adjacent, partly calcified matrix stained as intensely as the developing bone matrix (Fig. 2). Enamel matrix stained

Bone-Matrix Staining Reactions with Various Substrates

Substrate	Relative Intensity of Staining Reaction
1-naphthyl acetate	0
1-naphthyl propionate	0
6-bromo-2-naphthyl acetate	0
Naphthol AS-MX acetate	+++++
Naphthol AS-D acetate	++++
Naphthol AS-D chloroacetate	+++
Naphthol AS acetate	++
Naphthol AS-OL acetate	++
Naphthol AS-RT acetate	+

homogeneously, but the reaction was not as great as that of the dentin or bone.

Both bone marrow and dental pulp exhibited slight or no activity. However, with naphthol AS chloroacetate moderate activity of marrow was seen, in addition to intense staining of mast cells in the adjacent soft-tissue areas.

Partial or complete inhibition was produced by fluoride, benzethonium chloride, and benzalonium chloride. The other potential inhibitors had no effect. Sections pretreated with isoflurophate or E-600, followed by simultaneous coupling or post-coupling, showed only staining of bone and tooth structures. All other active tissues were unstained. (It was also found that 0.001 M concentrations of Cu^{++}, Cd^{++}, and Zn^{++} had a marked inhibitory effect.)

Of interest is the failure of naphtholic substrates other than those of the AS series to be hydrolyzed by the tissues studied. α-Naphthyl acetate, for example, is rapidly hydrolyzed by a number of tissues. It should be mentioned, however, that even with the most rapidly hydrolyzed AS substrates, the activity of bone matrix is of a relatively low order, probably about one-fourth of that observed in rat pancreas.

Phosphatase.—With both methods phosphatase activity was observed in the marrow spaces and the mesenchymal tissue associated with early matrix formation. The more calcified areas of bone spicules showed no activity. These observations of activity at the periphery of the matrix agree with previous findings.[2,3]

The dental pulp, odontoblasts, and their processes stained, while no reaction was present in either enamel or dental matrices.

Fig. 2.—Second molar tooth of 5-day-old mouse showing esterase activity of enamel matrix, dentin, and adjacent bone. Predentin and older dentin are inactive (AS-D acetate method). (*a*) bone; (*b*) enamel matrix; (*c*) dentin. Reduced to 8/9 of mag. × 160.

Summary

It would appear that the data presented suggest a genuine esterase activity of bone matrix. This activity was inhibited by

fluoride, quaternary ammonium, and certain metallic ions. The resistance to isofluorophate and E-600 bears further investigation. It should be mentioned that tissue esterase not sensitive to isofluorophate or E-600 has been observed.[8]

Several new derivatives of the naphthol AS series were shown to be useful substrates, and may also find application for demonstration of soft-tissue esterase.

Dr. William Alford and his group made the chemical analyses of the substrates; Dr. Jules Gladner, the samples of isoflurophate (DFP) and E-600.

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Large Congenital Aneurysm of the Right Coronary Artery

ENRIQUE VALDIVIA, M.D.; GEORGE G. ROWE, M.D., and D. MURRAY ANGEVINE, M.D., Madison, Wis.

The problem of aneurysm of the coronary arteries was adequately covered by Scott [1] in 1948, with a review of the literature and report of the largest aneurysm (10×8×8 cm.) of the coronary circulation until that time. He also suggested a classification and indicated that in his opinion many such aneurysms are of congenital origin.

The present case is reported because of the difficulties in diagnosis over a long period of clinical observation, as well as the large size (17×23×14 cm.) of the aneurysm, which seems best classified as of congenital origin.

Report of a Case

Clinical History.—The patient, a white woman, 25 years of age, was first admitted to the University Hospital on May 4, 1951. Her relatives stated that she had had a heart murmur since the age of 6 years; however, she associated her illness with a pounding of her heart about four years previously, during her first pregnancy. This palpitation was aggravated during the second pregnancy, and at the time of admission she could feel her chest heave with each heart beat. During recent months she had noted some dyspnea from climbing stairs and had awakened several times at night to assume a sitting posture in order to catch her breath. Digitalization had not been very helpful. No ankle edema had been present, nor were there symptoms suggestive of angina. Physical examination revealed a chronically ill patient who was quite comfortable in the recumbent position. A visible heave of the precordium was noted with each systole. The area of cardiac dullness was greatly enlarged, extending to the left anterior axillary line, while the cardiac impulse was in the fourth and fifth interspaces at the left midclavicular line. A loud, very harsh murmur was maximal near the apex but was transmitted widely over the precordium, and a middiastolic gallop was present at the apex. The lungs were clear. The firm, nontender liver was palpable 2 fingerbreadths below the costal margin. The electrocardiogram was compatible with posterolateral wall ischemia. Chest radiography, including fluoroscopy, revealed an extremely large cardiovascular shadow, which extended to the parieties on the left and completely hid the left hemidiaphragm and the lower portion of the left lung (Fig. 1). The cardiac mass depressed the diaphragm into the gastric air bubble. In the lateral view the cardiac density filled the anterior mediastinum. The barium-filled esophagus was generally displaced to the right and posteriorly, with no localized displacement to indicate enlargement of the left atrium. Hyperactive pulsation was noted along the right border and the left middle third, with rather shallow pulsation elsewhere. Angiocardiography in the anteroposterior projection (Fig. 2) indicated that the right-sided chambers were displaced toward the right and somewhat elevated. The left auricle was not enlarged, and, although the left ventricle was not certainly identified, it appeared to be displaced upward,

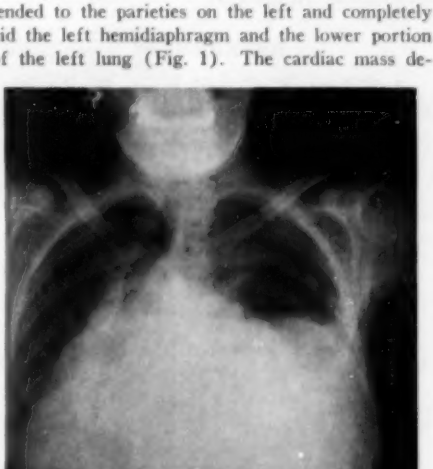


Fig. 1.—X-ray of chest demonstrating large cardiovascular shadow.

Submitted for publication Aug. 21, 1956.

Departments of Pathology and Medicine, University of Wisconsin Medical School.

Fig. 2.—Angiocardiography, anteroposterior view. Deviation to the right with some elevation of the right auricle and ventricle.

toward the right, and compressed. The rest of the "cardiac" shadow was formed by a large ovoid density occupying the lower left thorax, which did not become opaque in any of the films. It was, therefore, thought to be a large tumor or cyst arising from the heart or pericardium.

The patient was explored on May 17, 1951. There was some atelectasis of the lower part of the left lung from compression. A mass, almost filling the lower left thorax, was found within the pericardium. Several large unidentified vessels coursed over its surface. This mass pulsated paradoxically, and a thrill could be palpated on its surface, suggesting an aneurysm. Within a few minutes the lesion expanded considerably in size and appeared to be approximately 30 cm. in width and 15-20 cm. in length. Although a portion of the right side of the heart was identified, the left side was not, because of the large size of the mass. No line of cleavage could be found between the mass and the heart; so removal was not attempted. A needle was inserted through the thin wall into the tumor mass, and a stream of blood entered the syringe, confirming the impression of a very vascular tumor or aneurysm. The pericardium could not be closed because of the increase in size of the mass.

Postoperatively the patient did reasonably well except for severe pain in the incision, and was discharged from the hospital June 3, continuing to take digitalis. The intercostal neuralgia remained severe enough eventually to require neurectomy of the left sixth and seventh intercostal nerves.

Meanwhile there was no essential change in her previous difficulty of palpitation, fatigue, and dyspnea, even though a repeat chest x-ray, on July 18, 1951, showed a remarkable increase in the size of the tumor. Blood pressure was 120/70. Although she was never observed to be in heart failure at this hospital, she was treated for it by her local physician and on Jan. 13, 1954, was rebecause of persistent cardiac failure. She was ferred as an outpatient to the University Hospital treated with 15 mc. of radioactive iodine to reduce the tachycardia and dyspnea and stated that she felt better.

The final admission, on March 14, 1955, was for an acute psychotic episode, characterized by active hallucinations and a partially successful attempt to amputate her left ear. Physical examination revealed gross cardiomegaly. Systolic retraction of most of the precordium occurred except at the cardiac impulse. A very loud precordial double murmur was heard lateral and superior to the cardiac impulse in the third left interspace. Because of the marked depression and hallucinosis, a series of electroconvulsive treatments was undertaken. One hundred per cent oxygen was given for several minutes before and after each treatment. A course of 15 grand mal convulsions was given, without any significant cardiovascular effect but also without clearing of the psychotic state. The patient refused to eat or drink, becoming progressively weaker and more emaciated. A second course of shock therapy was started two weeks after completion of the first series. A grand mal convulsion was produced. Approximately one hour later she became restless and developed respiratory embarrassment with moist rales in the chest, followed by cyanosis and death within two hours.

At the time of death the diagnosis was not established with certainty; however, it appeared that she had either a very vascular hemangioma which by progressive growth had produced displacement and deformity of the heart or an aneurysm arising from the heart.

Autopsy.—The body is that of a well-developed young woman in a poor state of nutrition. Upon opening the chest, fibrous adhesions are demonstrated between the heart and the sternum; no pericardial cavity is demonstrated. The heart is rotated anteriorly to the right, due to a large globular tumor arising from the posterior wall of the left ventricle; this tumor pushes the heart and mediastinum 3 cm. to the right, is adherent to the diaphragm, and occupies almost completely the left pleural cavity, pushing the collapsed left lung upward (Fig. 3). There is 500 cc. of yellow fluid in the left thorax.

Heart: The heart, together with the mass, weighs 1800 gm. The mass has an external fibrotic capsule and measures 17 cm. across; the vertical diameter is 23 cm., and the surface of attachment to the posterior aspect of the heart

Fig. 3.—Anterior view. *RL*, right lung; *LL*, left lung; *RH*, right heart; *An*, Aneurysm.

covers about 90 sq. cm. This attachment begins in the right atrium posterior to the orifices of the venae cavae and extends along the posterior surface of the left ventricle parallel to the posterior longitudinal sulcus (Fig. 4). Upon opening the heart, all the cavities are seen to be moderately enlarged. The valves present some slight thickening, especially the mitral. Both ventricles have some subendocardial fibrosis.

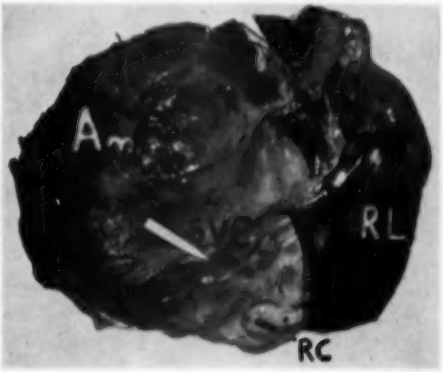
The right atrium is moderately enlarged (15 cm. in circumference). The wall of the atrium is 0.8 cm. thick at the crista terminalis and 0.2 cm. at the pectinate muscles. The valve of the coronary sinus is enlarged, measuring 3×2 cm. The orifice of the coronary sinus measures 0.2 cm. in diameter and is not occluded. Posterior to this orifice a 0.2 cm. opening communicates with the cavity of the large mass.

The left atrium is also dilated and measures 14 cm. in circumference; its posterior wall is adherent to the globular mass. The left ventricle presents some hypertrophy, and the mass is adherent to the posterior aspect of this ventricle.

Sections from the wall of the aneurysm present a fibrotic capsule that in some areas is calcified. There are, in addition, scattered, fragmented elastic fibers, suggesting that the aneurysm originated from an artery.

Coronary Arteries: The left coronary artery is apparently normal. The ostium of the right is 0.4 cm. in diameter. The vessel continues to the right descending branch as a tortuous and dilated vessel, 17 cm. in length and 1.3 cm. in transverse diameter (Fig. 5.) The wall of this artery is 0.1 cm. in thickness and ends in a saccular dilatation 4 cm. from the apex; the walls of this dilatation are calcified. This sac communicates freely with the cavity of the large mass already mentioned.

Fig. 4.—Posterior view. *RL*, right lung; *An*, aneurysm; *SVC*, orifice of superior vena cava; *RC*, dilated right coronary artery.



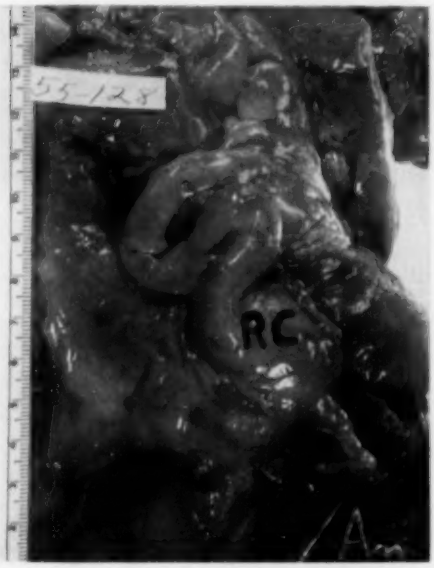


Fig. 5.—*RC*, dilated right coronary artery with saccular dilatation and communication with aneurysm (*An*).

Aneurysm: The large globular mass described in connection with the posterior aspect of the left ventricle and communicating with the right coronary artery contains thrombosed blood with typical laminations; the periphery of this clot is older,

and the most recent thrombosis is found near the site of the opening into the saccular dilatation of the right coronary artery; this area can be considered as a chamber, 6×5×5 cm., with a calcified wall and fairly smooth internal surface. There is a 0.2 cm. opening between this chamber and the right atrium. The entire large globular mass measures 17×23×14 cm. and can be considered as an aneurysmal dilatation of the right coronary artery with part of the blood which goes through the artery entering the right atrium through the described communication. No evidence of abnormal communication with the coronary veins is demonstrated.

The gross and microscopic examination of the remaining organs presented only fibrosis and atrophy of the thyroid gland and marked atelectasis of the left lung.

Summary

A case of a large aneurysm, probably congenital, arising at the terminal end of the right coronary artery and communicating with the right atrium, is reported.

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Sulfhemoglobinemia and Acute Renal Failure After Copper Sulfate Poisoning

Report of Two Fatal Cases

L. M. SANGHVI, M. R. C. P. (London), D. T. M. & H. (Eng.); R. SHARMA, M.D.; S. N. MISRA, M.B., B.S., and K. C. SAMUEL, M.D., Jaipur, India

Ingestion of large doses of copper sulfate is known to produce severe abdominal pain, vomiting, violent purging, cramps, hepatic necrosis, jaundice, acute hemolytic anemia, hematuria, convulsions, and death. The following two cases are considered worth reporting because after recovery from the usual symptoms of poisoning sulfhemoglobinemia developed in both, followed by acute tubular necrosis of the kidneys and death due to acute renal failure.

Report of Cases

CASE 1.—An 18-year-old youth was admitted to the hospital on the morning of Feb. 8, 1954, because of severe abdominal pain and vomiting, which began at 4 p.m. of the previous afternoon, soon after his taking a cup of tea. The vomited material was of a bluish color and often contained blood. On examination the patient appeared to be in great distress, due to persistent retching and vomiting. There was no evidence of dehydration, and his general condition was satisfactory, the pulse rate being 60 and respirations 17 per minute and the blood pressure 96/70 mm. Hg. There was generalized tenderness over the abdomen, most marked in the epigastrium. Blood examination showed a red cell count of 3,600,000, a white cell count of 8400 per cubic millimeter, with 73% neutrophils, 35% lymphocytes, and 3% mononuclear cells, and hemoglobin 12.5 gm. per 100 cc. Urine examination did not reveal any abnormality. The diagnosis of copper sulfate poisoning was confirmed on chemical examination of vomited material and gastric contents.

He was given potassium ferrocyanide, egg albumen, and milk orally and 500 cc. of 5% dextrose in isotonic saline intravenously. The progress of the patient was satisfactory, and he appeared to be all right on the morning of Feb. 10. The same evening, however, slight cyanosis became noticeable. On Feb. 11 the cyanosis was intense, with deep leaden-blue color of the skin and mucous membranes. He had a mild pyrexia, the temperature rising to a maximum of 100 F during the day. There was no dyspnea; examination of the cardiovascular and respiratory systems revealed no abnormality except slight tachycardia, and there appeared to be no evident cause for cyanosis. Spectroscopic examination of the blood, however, showed the typical band of sulfhemoglobin and revealed the cause of cyanosis. Urine diminished in quantity during the day, and examination revealed a specific gravity of 1.014 and the presence of albumin, red blood cells, leukocytes, and casts. Onset of acute renal failure was suspected, and the patient was treated for this complication on conservative lines. He had anuria after that evening. On Feb. 12 blood examination revealed a urea content of 120 mg. per 100 cc. He soon became drowsy and mentally confused, and by evening he was semiconscious, with the pulse rate 110 per minute, temperature 101 F, respirations 26 per minute, and blood pressure 86/60 mm. Hg. The condition deteriorated rapidly, and he died at 3 a.m. on Feb. 13.

CASE 2.—A 20-year-old youth was admitted to the hospital at 9 p.m. on Jan. 17, 1955, because of severe abdominal pain, diarrhea, and vomiting, which began at noon soon after lunch. He admitted taking about an ounce of copper sulfate with his lunch. On examination he was in a collapsed state with evident signs of dehydration, his pulse rate being 110 and respirations 20 per minute, temperature 97 F, and blood pressure 96/60 mm. Hg. There was generalized tenderness over the abdomen. Chemical examination of vomited material and gastric contents confirmed poisoning by copper sulfate. He was given the usual antidotes orally and 1500 cc. of 5% dextrose in isotonic saline intravenously. Next morning his condition was much better. He had four bowel movements and passed 450 cc. of urine during 12 hours after admission. Blood examination showed

Submitted for publication Aug. 7, 1956.

From the Departments of Medicine and of Pathology, S. M. S. Medical College and Hospital.

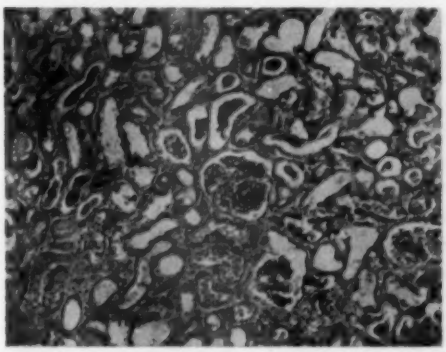


Fig. 1.—Glomerulus showing ischemia, and proximal convoluted tubules, showing dilatation with flattening of the epithellium but no evidence of necrosis. Reduced to 76.5% of mag. × 100.

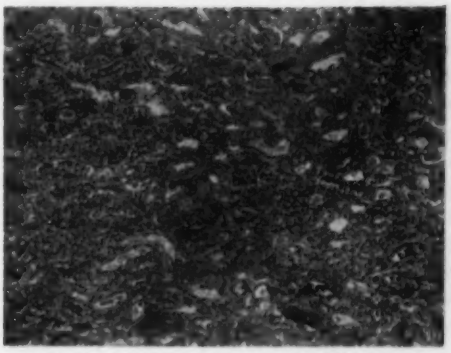


Fig. 2.—Interstitial cellular infiltration surrounding the necrotic tubules in the boundary zone. Reduced to 76.5% of mag. × 50.

a red cell count of 2,500,000, a leukocyte count of 4900 per cubic millimeter, with 64% neutrophils and 36% lymphocytes, and hemoglobin 8 gm. per 100 cc. Urine examination revealed no abnormality. His progress continued to be satisfactory, and on the morning of Jan. 20 he appeared to be well except for occasional hiccough; his pulse rate was 90 per minute, and blood pressure had risen to 115/70 mm. Hg. The urine excretion in the past 24 hours was 900 cc. In the afternoon, however, slight cyanosis was noticeable. On Jan. 21 the cyanosis was intense and he had mild pyrexia. Spectroscopic examination of the blood revealed the characteristic band of sulfhemoglobin. Urine diminished in quantity in the next 12 hours, and examination revealed a specific gravity of 1.013 and the presence of albumin, a large number of red blood cells, leukocytes, and casts. The diagnosis of complicating acute renal failure was made at this stage, and the patient was treated on conservative lines for this. His condition, however, gradually deteriorated. He had anuria on Jan. 22, and blood examination revealed a urea content of 200 mg. per 100 cc. Next day he became drowsy and mentally confused. On Jan. 24 he became semiconscious, his pulse rate being 100 per minute, blood pressure 110/80 mm. Hg, temperature 101 F, and blood urea 230 mg. per 100 cc. He died at 10:45 a.m. on Jan. 25.

Necropsy

At necropsy, in both the cases, significant changes were seen only in the kidneys and were similar. The kidneys were slightly enlarged and the capsules stripped easily. Cut sections showed a pale cortex and dark

Fig. 3.—Focal necrosis of the ascending loop of Henle and distal convoluted tubules. Right upper and left lower corners show normal tubules. Reduced to 76.5% of mag. × 100.

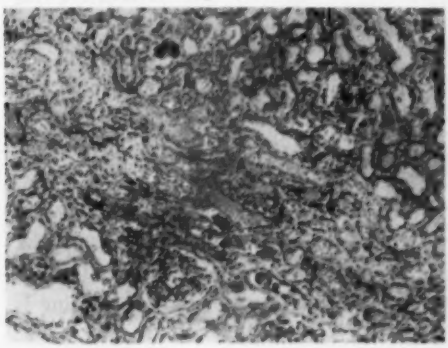
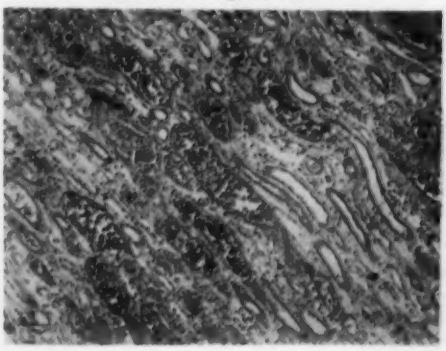


Fig. 4.—Medulla showing necrosis, interstitial edema and infiltration, and pigmented and unpigmented casts in some of the collecting tubules. Reduced to 76.5% of mag. × 100.



medulla. Microscopically (Figs. 1-4), glomeruli were normal in appearance, except a few, which showed minor changes in the form of ischemia and slight thickening of the basement membrane. Some of the proximal tubules showed cloudy swelling and degeneration of the epithelium, which was flattened where there was prominent dilatation, but no evidence of necrosis. The severest changes were seen in the ascending loop of Henle, the distal convoluted tubules, and the collecting tubules. They were focal in nature and consisted of areas of degeneration and necrosis of the epithelium with disruption of tubules. Numerous casts, some of them pigmented, were seen in the tubules, and often blocked the lumen. There were edema and cellular infiltration of the interstitial tissue surrounding these necrotic areas, particularly in the boundary zone.

Comment

The cases presented here have certain interesting features. They responded promptly to treatment, with marked improvement in their general condition, but 72 hours after ingestion of the poison cyanosis, which was demonstrated to be due to sulfhemoglobinemia, appeared in both of them. Sulfhemoglobinemia is known to occur after ingestion of the nitro and amino groups of drugs, most frequently after acetanilid, acetophenetidin (Phenacetin), and the sulfonamides.[1] Its formation probably depends upon the simultaneous presence of a catalytic reducing agent derived from the blood and of hydrogen sulfide formed in the intestine as a result of bacterial action. Constipation is reported to be usual in these cases,[2] though Brandenburg and Smith [3] noted it in only 20 of their 62 patients. In our cases, in the absence of ingestion of any drugs, there seems little doubt that copper sulfate poisoning in association with gastrointestinal upset was responsible for sulfhemoglobinemia. Copper is normally present in the red blood cells and the plasma. Lahey and co-workers [4] observed that the amount of copper in red cells was constant even under exceedingly pathological conditions associated with an increase in plasma copper. Gubler and co-workers [5] observed that when large doses of copper were given orally to dogs and intravenously to human beings there was a striking increase in plasma copper, a significant portion of which was taken up by the red cells. It seems possible that ingestion of large doses of copper sulfate in our cases may have given rise to an increased amount of copper in the red cells, which, acting as a catalytic reducing agent, in the presence of a gastrointestinal upset, led to the formation of sulfhemoglobinemia.

The second interesting feature was the occurrence of acute tubular necrosis and renal failure. Hematuria, suppression of urine, and parenchymatous inflammatory lesions of the kidneys have been described as the immediate complications of copper sulfate poisoning,[6] but no instance of acute tubular necrosis appears to have been reported in the literature. In both our patients evidence of renal failure was noticed 24 hours after the occurrence of sulfhemoglobinemia and consequent reduction of the oxygen-carrying capacity of the blood. At necropsy lesions which were severest in the distal nephron and which were distributed in a patchy manner were seen in the kidneys. Oliver [7] described two types of renal lesions in acute tubular necrosis: the first, a nephrotoxic necrosis, limited to the proximal convolution, which is functionally concerned with the handling of the poison, and the second, a disruption of the renal tubules, or tubulorrhexis, due to focal cortical ischemia. It was therefore most interesting to see this ischemic lesion in our cases, instead of the nephrotoxic one. From the presence of this type of lesion, it appears to us that anoxia due to sulfhemoglobinemia was the cause of acute tubular necrosis in our cases.

Summary

The occurrence of sulfhemoglobinemia and acute tubular necrosis of the kidneys in two cases of copper sulfate poisoning is reported. It is suggested that anoxia due

to sulfhemoglobinemia caused the acute tubular necrosis.

Dr. L. R. Sarin, superintendent, S.M.S. Hospital, gave us permission to report the cases.

10 Vivekanand Road.

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Mucormycosis of the Digestive Tract

ROGER DENIO BAKER, M.D.; DAVID E. BASSERT, M.D., Durham, N. C., and ELIZABETH FERRINGTON, M.D., Jackson, Miss.

Cases of mucormycosis involving the central nervous system [1] or the respiratory tract [2] have been reported recently in moderate numbers. A far rarer condition, however, is mucormycosis of the intestinal tract, of which there have been only three recorded cases. The first of these, reported by Paltauf [3] in 1885, described the fungus as gaining entrance to the body via the intestinal tract and spreading to the lungs and brain, resulting in death in coma. The second report, by Moore, Anderson and Everett,[4] in 1949, described a patient who died of peritonitis resulting from rupture of the cecum, following fungus infection and ulceration of the large bowel. The third report, by Martin and associates,[5] described mycotic esophageal ulceration in a fatal case of disseminated mucormycosis.

The purpose of the present paper is to report two new cases of mucormycosis of the digestive tract and to bring the subject up to date.

Submitted for publication Aug. 13, 1956.

Aided by Grant No. E-861 from the National Microbiological Institute, National Institutes of Health, U. S. Public Health Service, Department of Health, Education, and Welfare.

From the Department of Pathology, Duke University School of Medicine, and the Veterans Administration Hospital, Durham, N. C.; and from the University of Mississippi School of Medicine, and the Veterans Administration Center, Jackson, Miss.

Chief, Laboratory Service, Veterans Administration Hospital and Professor of Pathology, Duke University School of Medicine (Dr. Baker). Resident in Pathology, Veterans Administration Hospital, Durham, N. C. (Dr. Bassert). Since July 1, 1956, Dr. Bassert has been Assistant Pathologist, Lower Bucks County Hospital, Bristol, Pa. Assistant Chief, Laboratory Service, Veterans Administration Center, Jackson, Miss., and Clinical Instructor in Pathology, University of Mississippi School of Medicine (Dr. Ferrington).

Report of Cases

CASE 1.—A 43-year-old white man, tobacco warehouse laborer, had an hemoptysis of 60 cc. of dark-red blood nine weeks ante mortem. He was admitted to the Veterans Administration Hospital of Durham, N. C., March 10, 1955, 51 days ante mortem. The diagnosis of pulmonary tuberculosis with a cavity in the right upper lobe was established by demonstration of acid-fast organisms in the sputum and by roentgenographic studies. For the first four weeks he was treated with bed rest; isoniazid, 100 mg. three times a day, and aminosalicylic acid U. S. P., 4 gm. every six hours. On April 7 he developed a spiking fever, with a temperature of 102 F, which during the subsequent 11 days fluctuated between 100 and 105.8 F, rectally. His white blood cell count rose from 4100 per cubic millimeter to a high of 30,400, on April 18. Isoniazid and aminosalicylic acid U. S. P. were discontinued on April 8 because of possible toxicity to the liver, but these were reinstituted on April 12, and were finally discontinued on April 18, two days after the onset of jaundice. Treatment with cortisone, 12.5 mg., and tetracycline U. S. P. (Achromycin), 250 mg. every six hours, was begun on April 18 and was continued with Distrycin (equal amounts of streptomycin sulfate and dihydrostreptomycin sulfate), 1 gm. intramuscularly daily, and intravenous fluids for the duration of his illness. His fever abated on April 18 and did not recur until April 29, the day before death. He received two transfusions of whole blood on April 19. During the last two weeks of life the electrolyte values were about normal. On April 28 the cortisone was increased to 50 mg. intramuscularly every six hours. Terminally laboratory studies showed prothrombin 21%, bilirubin 14.6 mg. per 100 cc., thymol flocculation 4+, thymol turbidity 10.7 units per 100 cc., hemoglobin 7.4 gm. per 100 cc., and white blood cell count 16,200 per cubic millimeter, with 62 neutrophils, 27 stab forms, 8 lymphocytes, and 3 monocytes. On April 29 the patient passed a bloody stool and vomited coffee-ground material. He was again given a transfusion of 1000 cc. of whole blood, but he failed to improve and died early the next day, April 30.

At autopsy the body was well nourished but icteric. The peritoneal cavity contained 3000 ml. of xanthochromic fluid, and the intestine was dis-

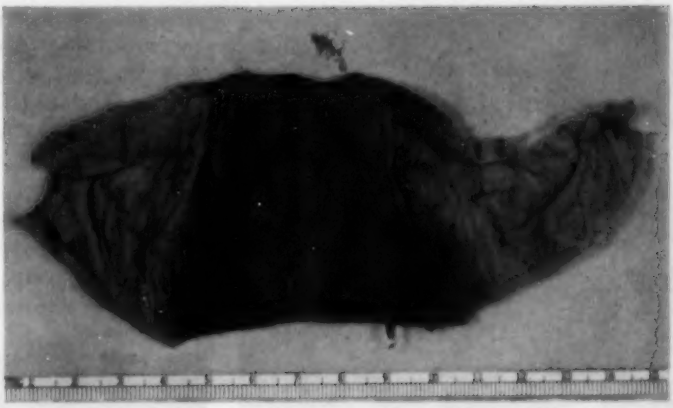


Fig. 1 (Case 1).—Intestinal mucormycosis. Segment of ileum showing focal area of hemorrhagic necrosis with central area of ulceration of necrotic mucosa.

tended and dark. Patchy areas of subserosal hemorrhage extended the length of the gastrointestinal tract. Massive adhesions obliterated the right pleural cavity, and 100 ml. of xanthochromic fluid filled the left pleural cavity.

Fresh blood filled the digestive tract from midesophagus to rectum. The distal two-thirds of the esophagus was ulcerated. In the posterior aspect of the fundus of the stomach there was a black ulcer, 2 cm. in diameter. At various intervals along the small and large bowel, but especially in the terminal ileum and cecum (Figs. 1 and 2), the entire wall was hemorrhagic and edematous and the mucosa partially ulcerated. The pelvic fat was hemorrhagic and contained thrombosed veins. Examination failed to reveal thrombosis of the main mesenteric, splenic, portal, or hepatic vessels.

The upper lobe of the right lung contained a smooth-walled cavity. Scattered encapsulated tubercles, 0.5 cm. in diameter, represented a bronchogenic spread of the tuberculosis in all lobes. The left lung was congested and edematous, but without active tuberculosis. The heart weighed 325 gm. and the spleen 200 gm.

The liver weighed 1225 gm. The free surface was jaundiced and smooth. The cut surface was jaundiced, with prominent lobular markings, like yellow halos, surrounding the hemorrhagic central regions. The biliary tract was normal. Both kidneys were jaundiced and enlarged, the left weighing 250 gm. and the right 220 gm.

Fig. 2 (Case 1).—Intestinal mucormycosis. Terminal ileum (above), ileocecal valve, and proximal cecum (lower left), showing areas of hemorrhagic necrosis.

Microscopic sections failed to reveal fungi in the regions of ulceration of the esophagus or in the ulcer of the stomach. However, there were numerous branched, nonseptate hyphae, 6μ-12μ in diameter, in the vessels of the serosa overlying the gastric ulcer. Similarly, at various levels of the small and large intestine the fungus was found in the serosal vessels and surrounding fatty tissues (Fig. 3). The fungi grew in the walls of both arteries and veins, tending to parallel the concentric pattern of muscular fibers. When numerous hyphae were found within the lumens, the vessels were usually thrombosed, and the adjacent bowel wall was hemorrhagic, necrotic, and infiltrated with

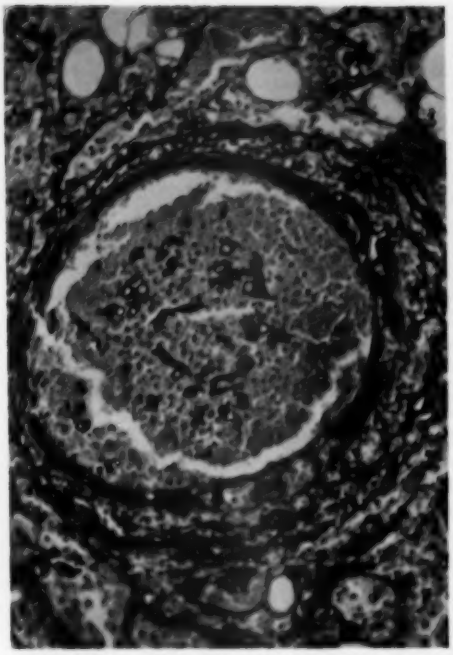
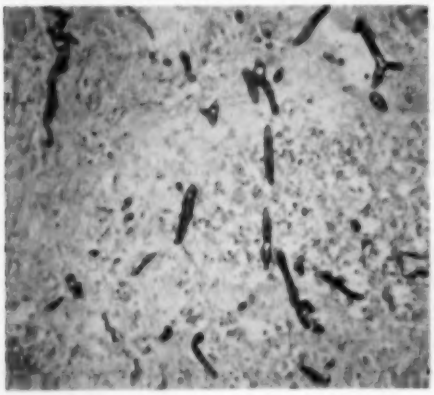


Fig. 3 (Case 1).—A thrombosed mesenteric vessel showing hyphae in the lumen, wall, and surrounding tissue. Methenamine silver nitrate stain; reduced to 44% of mag. × 254.

neutrophils, apparently the result of infarction. Necrotic mucosa was often associated with heavy fungus growth, while viable mucosa was only rarely involved.

Caseous tubercles and acid-fast bacilli were observed in sections of the right lung.

Fig. 4 (Case 1).—Necrotic liver and hyphae. MacCallum bacterial stain; × 127.



Features common to both lungs included congestion and edema; no fungi could be demonstrated. Sections of the liver showed loss of hepatic parenchyma due to recent massive necrosis. All liver cells had disappeared about the congested central regions, and only islands of viable cells persisted about the portal areas. Necrotic cell masses and polymorphonuclear neutrophils and lymphocytes were present in moderate numbers. There was proliferation of bile

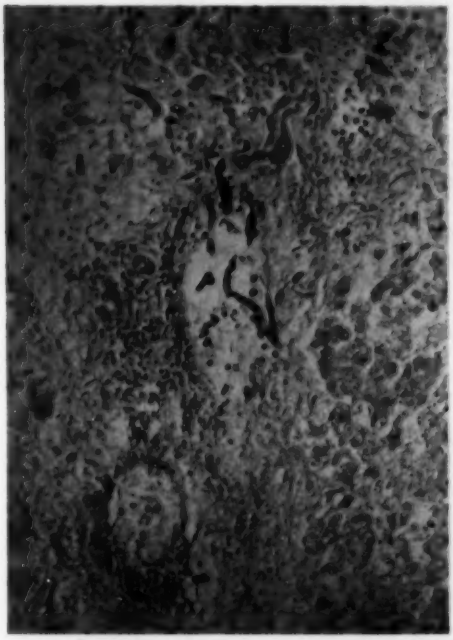


Fig. 5 (Case 1).—Liver portal triad. Fungi in portal vein and adjacent tissue. Methenamine-silver nitrate stain; reduced to 44% of mag. × 254.

ducts but no fibrosis. In one portion of the liver there was a focus of complete necrosis, 1 cm. in diameter, containing fungus hyphae (Fig. 4). The filaments were present also in veins and arteries (Fig. 5). The fungi were clearly demonstrated by hematoxylin-and-eosin stain and by MacCallum's bacterial stain. Sections of the kidney showed bile casts and arteriolosclerosis.

Anatomical Diagnosis.—Fibrocaseous and cavitary tuberculosis of right lung; subacute

hepatitis of unknown cause; jaundice; gastrointestinal mucormycosis with infarcts, ulceration, and hemorrhage. Acute esophagitis; pulmonary congestion and edema; bile nephrosis; arteriolosclerosis of kidney.

Comment.—In Case 1 there was extensive mucormycosis of the gastrointestinal tract, minimal mucormycosis of the liver, and none elsewhere in the body.

Apparently the fungus invaded the intestinal wall from the lumen and produced thrombosis of the small mesenteric vessels of the serosa. The fungus reached the liver by the portal blood stream and produced a small focus of infection there. The absence of fungus infection in other parts of the body indicates that the fungus was not disseminated to the gastrointestinal tract via the mesenteric arteries. Intramural hemorrhages of the intestine due to hepatic insufficiency may have been the first event, followed by secondary fungus infection of devitalized tissues. The extension of the infection to small mesenteric vessels then led to intestinal infarction. Death was due to extensive intraluminal hemorrhage.

In mucormycosis of the lungs or central nervous system there is usually a predisposing disease, such as diabetes or leukemia. The predisposing condition in this case, involving the digestive tract, was hepatitis, probably of toxic origin. A viral or unknown cause could not be excluded. However, the antituberculous drugs, either singly or in combination, may have injured the liver, for aminosalicylic acid [6] and isoniazid [7] cause hepatic damage on rare occasions. Antibiotics, chiefly in the form of tetracycline, were administered for several weeks, while cortisone was given during the last 12 days of life. Both these therapies favor mycotic invasion.[8]

CASE 2.—A 75-year-old white man was admitted to the Veterans Administration Center, Jackson, Miss., 12 days ante mortem, because of the sudden onset of severe, nonradiating pain in the right lower quadrant. There was a five-year history of angina, for which he had been hospitalized many times, and on the day of admission he had had two anginal attacks.

The patient was well nourished and acutely ill. There was tenderness in the right lower quadrant on both abdominal and rectal examination. A systolic murmur was heard over the enlarged heart.

Urinalysis on admission showed 2+ albumin, a rare white blood cell, and rare hyaline and granular casts. The white blood cell count was 15,600 per cubic millimeter, with 71 neutrophils, 10 band forms, and 19 other forms. Blood urea nitrogen was 16 mg. per 100 cc.; CO_2, 21 mEq. per liter; sodium, 128 mEq. per liter; chlorides, 101 mEq. per liter. A chest film demonstrated an enlarged heart, and a tortuous, dilated aorta. An electrocardiogram showed complete right bundle-branch block.

Because of the poor renal and cardiac status, the patient was treated conservatively with massive doses of antibiotics. At first the abdominal symptoms improved. However, because of intravenous administration of dextrose and water and a low-salt intake, his serum sodium and chloride values fell. Intravenous saline was then given, and he developed edema of the feet. His blood urea nitrogen rose to 67 mg. per 100 cc., and his blood pressure fell. He became increasingly stuporous and died 12 days after admission.

At autopsy there was pitting edema of the dorsum of the hands and feet. Cloudy, yellow fluid, measuring 200 ml., was found in the peritoneal cavity, and a like amount of similar fluid was found in each pleural cavity.

In the cecum and ascending colon there was an area, 6×6 cm. in diameter, of swollen, hemorrhagic, infarcted bowel. Fibrin covered the serosa of this area. The appendix was normal.

The heart was enlarged (570 gm.), and there were numerous gray scars in the posterior wall of the apex near the septum. The right coronary artery was narrowed by arteriosclerosis. In the atherosclerotic aorta there was a large abdominal aneurysm, containing a laminated thrombus. The right and left lungs weighed 960 and 860 gm., respectively. The right middle and lower lobes and the left lower lobe were consolidated extensively. The liver was fatty and the lobular markings indistinct. Both kidneys showed reduction of parenchyma. The prostate was enlarged. The mucosa of the urinary bladder was trabeculated and the urine cloudy.

Microscopic sections of the hemorrhagic lesion of the large intestine presented remnants of necrotic mucosa, infiltrated with hyphae, 6μ-15μ in width (Fig. 6). The submucosa was edematous and necrotic, with many hyphae. The smooth muscle of the muscularis was densely infiltrated with the

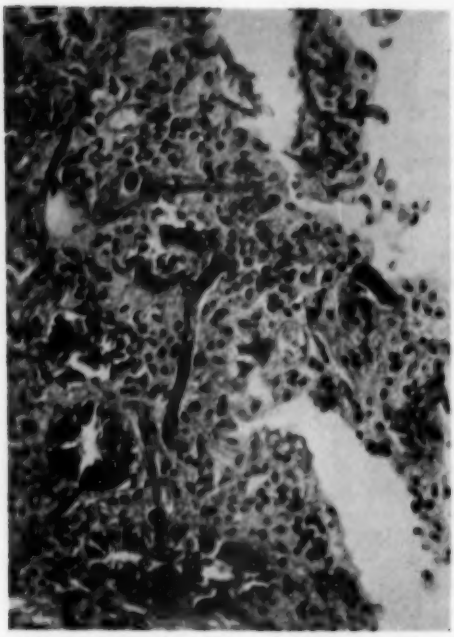


Fig. 6 (Case 2).—Hyphae in intestinal mucosa. Hematoxylin and eosin stain; reduced to 44% of mag. × 368.

fungus, and there was necrosis of muscle fibers and much polymorphonuclear cell response. Serosal arteries and veins contained hyphae. Sections of the esophagus showed nonmycotic chronic inflammation and mucosal necrosis.

The lungs showed extensive confluent bronchopneumonia in the consolidated lobes, with many Gram-positive cocci in the neutrophilic exudate, but no fungus. The myocardium was extensively scarred. The central portions of the liver lobules were congested, and many hepatic cells contained fat vacuoles. There was also moderate periportal lymphocytic infiltration, and many bile ducts were plugged with inspissated bile.

Anatomical Diagnoses.—Cardiac hypertrophy, coronary arteriosclerosis, healed myocardial infarct; anasarca; chronic passive congestion of liver and spleen. Mucormycosis of cecum and ascending colon with mycotic arteritis and phlebitis and hemorrhagic infarction; localized fibrinous peritonitis of cecum and ascending colon. Lobular pneumonia; chronic esophagitis. Arteriosclerotic aneurysm of aorta. Diverticulosis of sigmoid colon. Benign prostatic hypertrophy. Arteriolonephrosclerosis.

Comment.—In Case 2 there were symptoms, 12 days before death, suggesting acute appendicitis. At autopsy it was demonstrated that the symptoms had been due to mucormycosis of the large intestine, like that of the first case, but more circumscribed. As in the first case, the fungus apparently entered the wall of the cecum and ascending colon from the lumen. Unlike the first case, there was no massive hepatic damage and no jaundice or prothrombin deficiency. Thus, no predisposing disease could be defined. The patient died in uremia with lobular pneumonia, which developed as a complication of the intestinal mucormycosis.

General Considerations

Survey of Cases.—Tabulation of the five reported cases of mucormycosis of the digestive tract (Table) indicates that the condition has been observed in various parts of the United States and in Europe. The ages of the patients have varied from 2½ to 75 years. The duration of the mycosis, estimated from the clinical course, varied from 3 to 17 days. The lesions were found in the esophagus once, in the stomach once, in the small intestine twice, and in the large intestine three times. In the three previously reported cases the lesions were less like infarcts than in our two cases, but ulceration was present in all. The mycosis of the digestive tract was an important factor in causing death, except in the case of Martin and associates,[5] in which the esophageal lesion was part of a disseminated mucase, of cerebral type, the digestive tract was the portal of entry of the fungus.

Predisposing Conditions.—Contrary to what has been observed in cerebral[1] and cormycosis. With the exception of the same pulmonary mucormycosis,[2] there was no in-

Mucormycosis of the Digestive Tract

Author	Age	Race Sex	Residence	Duration of Mycosis, Days	Location of Lesions	Cause of Death
Paltauf[3]	52	White M	Austria	17	Terminal ileum	Mycotic septicemia
Moore, Anderson, & Everett[4]	37	White F	Wisconsin	15	Large bowel	Peritonitis
Martin et al.[5]	2½	White M	Texas	8	Esophagus	Disseminated mucormycosis
Case 1	43	White M	N. C.	2	Stomach, small intestine, and large intestine	Intestinal hemorrhage
Case 2	75	White M	Miss.	12	Proximal colon	Terminal pneumonia

stance of prior diabetes mellitus or leukemia in these five cases. In three cases there were no evidences of a predisposing condition. In our first case the subacute hepatitis and jaundice, antibiotic therapy, and cortisone are all possible predisposing conditions. In the case of Martin and associates[5] diarrhea, severe electrolyte imbalance, chemotherapy, and parenteral fluid administration antedated the symptoms of the mycosis and may have acted as predisposing factors.

The Fungus.—The fungus had the same appearance in tissue sections in the case of Martin and associates[5] as it did in our two cases, as well as in the cases of cerebral mucormycosis from which Rhizopus has been recovered culturally.[9,1] The filaments in tissue were broad, branching, nonseptate hyphae, varying from 6μ-20μ in width.

In the case of Moore, Anderson, and Everett[4] the organisms were of about the same thickness but presented an almost fanlike branching pattern in some regions. In Paltauf's case the hyphae were thinner, from 3μ-6μ in diameter, and knobby, while there were spores in tissue. Mucor corimbifer was suggested as the probable type of fungus. In both these cases abscesses were prominent features, while in our cases and in that of Martin and associates[5] there were no abscesses, and infarct-like lesions predominated, as in cerebral and pulmonary cases. These considerations suggest that the five cases of mucormycosis of the digestive tract may have been caused by different fungi of the nonseptate type. In all five cases, however, the fungus invaded blood vessels, a finding highly characteristic of mucormycosis of the cerebral and pulmonary forms.

Summary

Two new cases of mucormycosis of the digestive tract are presented, making a total of five reported cases.

The disease occurred at all ages and had a duration of 3 to 17 days, leading to death.

Predisposing conditions in the form of diarrhea, subacute hepatitis, and antibiotic and cortisone therapy may have favored the infection in two cases.

The lesions consisted of ulcerations in all parts of the digestive tract, with predilection for the terminal ileum and large intestine. In all cases the fungus invaded blood vessels, and in several produced thromboses and infarcts.

The fungus in tissues consisted of branching, nonseptate hyphae from 3μ to 20μ in width, similar to the organisms of cerebral and pulmonary mucormycosis. Though the fungus was not cultured in any case, Rhizopus was probably the commoner causative fungus, Mucor the less common.

VA Hospital, Fulton St. and Erwin Rd.

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Peliosis Hepatis

Report of a Case

ALBERT E. W. TRITES, M.D., C.M., Vancouver, B. C., Canada

Peliosis hepatis may be defined as an unusual morphologic change in the liver wherein that organ contains a profusion of minute, cyst-like, blood-filled cavities. The etiology and pathogenesis of the condition are uncertain, and it is thought to have no clinical significance.

Sporadic instances of peliosis hepatis have appeared in the German literature since the time of Wagner's initial report, in 1861. When Zak [1] reviewed the literature in 1950, he was able to compile 30 cases in all and added to these a case of his own, which was, incidentally, the first report in the English-speaking literature. Zak alluded to one other case, and since the appearance of his article seven other instances have appeared in print.[2-4] Of the 38 known cases of peliosis hepatis reported up to now, all but 6 occurred in patients who had suffered from tuberculosis. In fact, Young,[4] who added 3 cases to the literature, ventured the opinion that peliosis hepatis was a reasonably common condition in tuberculous persons; his 3 cases came to light from postmortem examinations of 15 consecutive deaths from tuberculosis. The patients who did not die of tuberculosis suffered variously from carcinoma of stomach, rectum, or cervix; pyonephrosis; diabetes mellitus, and polyserositis.

Irrespective of the cause of death, the morphology of the liver was similar in all cases. The livers were of average size, and their general configuration was not disturbed. Examination of the capsular surface of the liver revealed the presence of small dark circular areas, which corresponded, on the cut surface, to cystic, blood-filled spaces. In general, these cysts averaged 1-2 mm. in diameter. Microscopically, the cysts varied from round to oval, or were irregular in outline. In some instances the cysts appeared to bear a direct relation to central vein areas,[4] but the usual observation was that these foci bore no constant relationship to the liver lobules. Free communication with the sinusoids was frequently remarked upon. The contents of the cysts were generally noted to be whole blood which had separated into a cellular and a fibrin layer, and Zak mentioned margination of the leukocytes. Although Hamilton and Lubitz [2] use the term "thrombosis," their description does not seem to fulfill criteria necessary for the use of this term, and other authors mention that no organization of the blood had taken place. Hamilton and Lubitz note that an endothelial lining could be identified in most cysts, but Burger and Marcuse [3] state that the cysts "lacked any endothelial or fibrous tissue lining." Zak noted that the borders were formed by liver cells but that occasionally endothelium could be seen; this, he believed, was merely a remnant of the original sinusoid. Compression, atrophy, and necrosis of surrounding parenchymal cells were noted in several instances,[1-2] and foci of necrosis of liver cells in the absence of peliosis were noted by some.[1,4] Sclerotic foci were found in one instance,[2] and this was interpreted as a healing phase following thrombosis.

Report of Case

This 55-year-old white man was first admitted to the Vancouver General Hospital in October, 1954, for elective repair of bilateral indirect in-

Submitted for publication Aug. 20, 1956.

From the Department of Pathology, Vancouver General Hospital.

guinal hernia. Functional inquiry at that time elicited a vague complaint of right flank pain which had been present for about one year. Urinalysis showed 3+ protein, 1+ white blood cells, and 2+ red blood cells. When cystoscopy and pyelography failed to reveal any abnormality, he was discharged following his herniorrhaphy.

Eighteen months later he was readmitted to this hospital with a diagnosis of uremia. Inquiry on admission revealed complaints of passing cloudy urine for about one year and severe general malaise with weakness and tiredness for about two weeks. Examination at this time showed the patient to be chronically ill and mentally dull. There was some deep tenderness in the right flank, but no mass could be defined. Throughout this terminal hospital stay, the patient's blood NPN ranged between 212 and 265 mg. per 100 cc. Hemoglobin was always in the range of 6 to 6.5 gm. per 100 cc. Urinalyses repeatedly showed 3+ protein, 4+ white blood cells, 2+ pus cells, and 1+ red blood cells. Management consisted chiefly of manipulation of the patient's fluid and electrolyte intake, but despite these measures he became increasingly restless, and terminally his respirations were wheezing and labored. He died on March 26, 1956.

Necropsy Findings

The body measured approximately 5 ft. 10 in. (177.8 cm.) in length and weighed roughly 210 lb. (95.3 kg.). There was pronounced obesity, in addition to a marked degree of generalized edema.

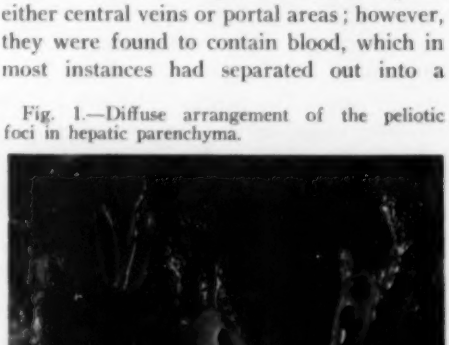
Pleural Cavities.—The pleural cavities contained approximately 1500 cc. of clear, pale fluid on either side.

Lungs.—The lungs were heavy (1250 and 1150 gm.) and were profoundly edematous. There was a minor degree of superficial atelectasis. Microscopically, the edema and collapse could be seen, but, in addition, alveoli were lined by fibrinous hyaline membranes suggestive of uremic pneumonitis. No evidence of tuberculosis was seen either in the gross or microscopically.

Kidneys.—Each kidney weighed 275 gm., and they were generally similar in appearance. Each kidney contained a multitude of cysts, ranging from pinhead-sized to several centimeters in diameter. The subcapsular cortical surfaces not involved by cysts showed alternating areas of hyperemia and ischemia, but little could be seen on the cut surfaces to suggest active inflammation. The renal calyces and pelves were grossly normal, as were the ureters and bladder. Microscopically, the most striking change was in the glomeruli, where increased cellularity of tufts and adhesions between tufts and Bowman capsules could be seen throughout all sections. There was a tendency toward crescent formation. The tubular elements were, relatively speaking, normal. Many cystic cavities could be seen, and these contained deeply staining eosinophilic material and were lined by flattened cuboidal epithelium. These findings were interpreted as subacute glomerulonephritis, superimposed on multicystic kidneys. It was considered that the cysts were of an acquired rather than a congenital nature.

Liver.—This organ weighed 2400 gm. and was normal in over-all configuration, although somewhat pale in color. Examination of the capsular surfaces revealed a myriad of pinhead-sized dark dots, which, when the liver was sectioned, were found to correspond to minute cystic cavities, approximating 3 mm. in diameter. These cysts contained a dark red-brown fluid (Fig. 1). Microscopically, the hepatic parenchyma was within normal limits except for the presence of a minimal degree of centrilobular congestion. The cystic areas noted in the gross bore no constant spatial relationship to either central veins or portal areas; however, they were found to contain blood, which in most instances had separated out into a

Fig. 1.—Diffuse arrangement of the peliotic foci in hepatic parenchyma.



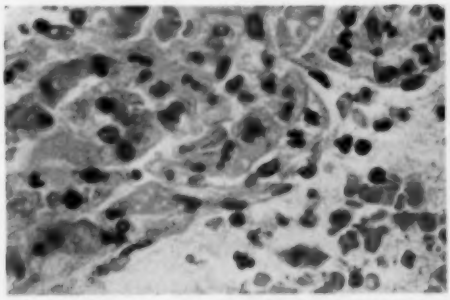


Fig. 2.—Blood cells entering a sinusoid from a peliotic cyst. The endothelial lining of the cyst may also be seen.

layer of intact cellular elements and a layer of fibrin. The leukocytes tended to be marginated, but no evidence of thrombosis was seen. The spaces were found, for the most part, to be lined by flattened endothelial cells. Many instances of communication between the cysts and the sinusoidal spaces could be seen (Fig. 2). Outside the endothelium, the cyst wall consisted of a variable amount of fibrous connective tissue. No elastic tissue was demonstrable. The hepatic parenchyma surrounding the peliotic foci tended to appear somewhat compressed, but actual necrosis was not a pronounced feature.

Other Findings.—The other viscera were normal.

Anatomic Diagnoses.—(1) Peliosis hepatis; (2) subacute glomerulonephritis; (3) multicystic kidneys; (4) bilateral pleural effusions; (5) pulmonary edema and atelectasis; (6) generalized anasarca.

Comment

The "American Illustrated Medical Dictionary" (Dorland) equates peliosis with purpura and defines the latter as "a disease characterized by the formation of purple patches on the skin and mucous membranes, due to subcutaneous extravasation of blood." All the recent reports of peliosis hepatis tend to emphasize the fact that the blood elements are not degenerate in the cystic spaces and that these spaces communicate with the sinusoids. These factors lend emphasis to the thought that peliosis hepatis is something of a misnomer. However, despite the rarity of this entity, its name is now well established in the literature, and any suggestion that it should be rechristened "telangiectasis hepatis," or something else, would be apt to meet with little favor.

The etiology of this condition is still obscure, but several theories have been offered. Zak [1] summarized these as follows: (1) congenital malformation, (2) vascular varicosities with or without preceding angiitis, (3) ruptured vessels with or without inflammation, (4) primary focal hepatic necrosis followed by local hemorrhage, or (5) a combination of local hepatic necrosis and angiitis with bulging of the vessels into the softened parenchyma. He believed that the last theory was the most likely and that the hepatic necrosis was on a toxic basis (toxin unknown). Hamilton and Lubitz emphasize the high incidence of tuberculosis and peliosis hepatis and believe that the focal necrosis was actually due to the chronic venous congestion plus some unknown factor (which could be a toxin). The necessity of postulating some unknown factor is understandable when one remembers the infinitely high incidence of both venous congestion of the liver and pulmonary tuberculosis as compared with the infrequent reports of peliosis hepatis. The rarity of the latter condition is underlined by the fact that between 1200 and 1300 postmortem examinations are performed annually at the Vancouver General Hospital and, except for the presently reported case, no similar instance is recorded in the files over the past eight years. Not having seen some of the lesions noted by the other authors (the necrotic and sclerotic foci, the thrombosed channels, the tuberculosis, the preponderance of plasma cells,[1] and the profound centrilobular congestion and necrosis), we find that we are unable to venture more than a guess as to pathogenesis. It is difficult to understand why peliosis hepatis could not be classified as congenital in nature, but even

in that event some element, as yet unknown, must be postulated to explain the high association with tuberculosis, despite the fact that no such association was found in our case.

Summary

Peliosis hepatis is an unusual pathological entity in which the liver contains many minute blood-filled cystic spaces. It would appear to be an extremely unusual finding and one with no apparent clinical significance.

A case is discussed in which peliosis hepatis was an incidental finding at autopsy in a 55-year-old man who died of subacute glomerulonephritis superimposed on multicystic kidneys.

The English literature is briefly surveyed.

Vancouver General Hospital (9).

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News and Comment

PERSONAL NEWS

Dr. A. James French Appointed Chairman in Pathology at University of Michigan.—Dr. A. James French has been appointed chairman of the department of pathology at the University of Michigan Medical School, succeeding Dr. Carl Weller, who retired on July 1, 1956.

Lewis A. Conner Memorial Lecture Given by Dr. Jesse E. Edwards.—Dr. Jesse E. Edwards, of the Department of Pathology of the Mayo Clinic, gave the Lewis A. Conner Memorial Lecture at the annual meeting of the American Heart Association in Cincinnati, on Oct. 27. His subject was "Functional Pathology of the Pulmonary Vascular Tree in Congenital Cardiac Disease."

Dr. Henry C. Sweany Awarded Medal.—Dr. Henry C. Sweany, director of research of the Missouri State Sanatorium, in Mount Vernon, recently was awarded the annual medal of the American College of Chest Physicians for outstanding contributions in relation to pathology of the chest.

Dr. Benjamin Markowitz Dies.—Dr. Benjamin Markowitz, of Bloomington, Ill., past-president of the Illinois Society of Pathologists, died on Sept. 17, at the age of 60, of carcinoma of the prostate gland.

ANNOUNCEMENTS

Mexican Society of Pathologists.—The Mexican Society of Pathologists met in Mexico City on Nov. 17. The seminar was conducted by Dr. Franklin M. Foote, of Memorial Center for Cancer and Allied Diseases, New York.

Carl V. Weller Lecture.—Dr. Howard T. Karsner will present the Carl V. Weller Lecture of the Michigan Pathological Society at Ann Arbor on Dec. 8. His subject will be "The Place of Pathology in Biomedical Research."

Wisconsin Society of Pathology.—The Wisconsin Society of Pathology held its fall meeting in Milwaukee on Nov. 12. Dr. Milton G. Bohrod, of Rochester General Hospital, Rochester, N. Y., moderated the meeting dealing with "Collagen Diseases and Related Conditions." At the evening meeting Dr. John Z. Bowers, dean of the University of Wisconsin Medical School, spoke on "Changing Concepts in the Teaching of the Basic Sciences."

Seventh International Cancer Congress.—The Seventh International Cancer Congress, sponsored by the International Union Against Cancer, will be held in London, England, July 6-12, 1958, under the presidency of Sir Stanford Cade. Congress headquarters will be The Royal Festival Hall.

There will be two main sessions of the Congress:

A. Experimental
B. Clinical and Cancer Control

Special emphasis will be placed on Hormones and Cancer, Chemotherapy, Carcinogenesis, and Cancer of the Lung.

Proffered papers will be considered only if submitted with an accompanying abstract (not over 200 words) before October, 1957, and if dealing with new and unpublished work.

The registration fee for the Congress will be £10, or $30, and the latest date for registration without late fee will be Jan. 1, 1958.

Registration forms and a preliminary program will be available early in 1957 on application to The Secretary General, Seventh International Cancer Congress, 45 Lincoln's Inn Fields, London, W. C. 2, England.

Forty Faculty Awards for Research in Biology for Summer of 1957.—The Lalor Foundation announces details of the 40 awards which it is offering to younger college and

university staff and faculty members for research in the biological sciences for the summer of 1957. This is the third annual series of such summer research awards.

The awards are for advanced study and research employing chemistry or physics to attack problems in any field of biology. The studies may be carried on at any institution of the award holder's choice. The upper age limit for appointment is 40 years.

The awards will usually not exceed $900 for a single man or woman, $1100 for a married person working at his home institution, and $1250 for a married person whose principal program is at another institution. Transportation and other expenses are for the account of the award holder.

Younger faculty members with important teaching obligations find in many cases that the summer months between the academic years are the only uninterrupted periods available to them for carrying on fundamental research of their own choosing. The Lalor Faculty Summer Research Awards are designed to assist such men and women and thereby add to their standing as scientists and effectiveness as teachers.

In recent years the Foundation has maintained a number of postdoctorate summer fellowships at the Marine Biological Laboratory at Woods Hole, Mass. With the consolidation of these fellowships into the present program, it is suggested that men and women interested in work at M. B. L., and eligible under the Lalor faculty summer award plan, should submit applications under this newer program.

Inquiries respecting Lalor Faculty Summer Research Awards should be addressed to C. Lalor Burdick, director of the Lalor Foundation, 4400 Lancaster Pike, Wilmington 5, Del. Final date for receipt of completed applications is Jan. 14, 1957, and notification regarding appointment may be expected by March 15, 1957.

Books

The Biochemistry and Physiology of Bone. By Geoffrey H. Bourne. Price, $20.00. Pp. 875, with 366 illustrations. Academic Press, Inc., 125 E. 23d St., New York 10, 1956.

This book consists of a series of papers by widely known authors from America, Europe, and the Middle East. There are chapters on the general anatomy and histology of bone, mechanical investigations of bone, ground substances, organic matrix, collagen fibers, ultrastructure, the osteoblast, the osteoclast, phosphatase, the chemistry of calcification, and citric acid. There are autoradiographic studies of bone formation and growth, several chapters on development and growth of bone, and a consideration of repair and transplantation of bone. There is a chapter on each of the vitamins and endocrines which affect bone. The final chapters are on radiation changes and pathological calcification.

There are the inevitable overlap of material and variation of readability from chapter to chapter that is to be expected in a book with twenty-four chapters by twenty-eight authors. Material is drawn from a wide range of sources. Its comprehensiveness will make it valuable as a reference work for many specialists. It gives perspective to the older work and interpretation and detailed references to recent research. The rather high price will restrict the popularity of this detailed consideration of the biochemistry and physiology of bone.

Cancer: A Manual for Practitioners. Third Edition. By American Cancer Society (Massachusetts Division), Inc. Price, $2.00. Pp. 319. American Cancer Society (Massachusetts Division), Inc., 462 Boylston St., Boston 16, 1956.

The third edition of this book, which was first published in 1940, represents the bringing up to date of material which was last reviewed six years ago. In this edition all the chapters have been revised and some new chapters added. In the fifty chapters the material is presented in a condensed manner with the purpose of conveying to all interested in the advances in the cancer field newer information, particularly of practical value. The Manual is designed primarily for the use of practitioners in the early diagnosis of cancer. The contributors are all well-known students of various phases of cancer. The publication was made possible by a grant from the Massachusetts Division of the American Cancer Society, Inc., thereby insuring the low cost of $2.00. The book should be useful to cancer coordinators and to teachers in medical schools. There are no illustrations, but it is carefully indexed.

Essays in Biochemistry. By Samuel Graff, editor. Price, $6.50. Pp. 345, with 54 figures. John Wiley & Sons, Inc., 440 4th Ave., New York, 1956.

These essays were written in honor of Hans Thacher Clark by his students or associates. The book honors a distinguished scientist by assembling these concrete examples of the extent and worth of his influence.

To this reviewer the essays by Graff, Borek, and Evans were especially interesting. S. Graff outlined certain problems relative to cancer, discussing the possibility that viruses may be causative agents in some types of cancers and that some of the anticancer drugs, such as 8-azaguanine, are also antiviral. E. Borek pointed out that Escherichia coli K_{12} and some other organisms carry a low-order ability to produce bacteriophage. Following irradiation or chemical induction, however, the resulting phage progeny multiplies to the extent that the host is completely destroyed. Only if a starvation medium is used prior to irradiation and then replaced does the organism lose the power to produce these large quantities of phage. Testing various metabolites revealed the interesting fact that inducing power elicited by irradiation resides in the pteridine residue of Leucovorin. E. A. Evans Jr. discussed the biochemistry of bacterial viruses in a thorough manner, emphasizing the several stages involved in a biochemical process, extending from the motivation for research arising

in human pathology and reaching to the molecular explanation at the very heart of the problem.

Most biologists wish to gain familiarity with the various branches of their general field. They prefer to do this under the tutelage of the leaders in the different subject areas. The "Essays in Biochemistry" should serve well as one of the textbooks for this type of study.

Clinical Pathology, Application and Interpretation. Second Edition. By Benjamin B. Wells. Price, $8.50. Pp. 488. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1956.

As the author states, this is an "entirely practical," condensed selective treatment of the rapidly expanding field of clinical pathology. Emphasis throughout is on indications and interpretations. Discussion of technique is limited to a concluding chapter, which deals only with the common office laboratory procedures. Fundamental biochemical concepts are beyond the scope of the book. As such, it is of limited value to the practicing pathologist and the student of disease. It is perhaps best suited for the family physician.

This second edition includes much new and expanded material, including discussions of viral and rickettsial diseases, hypersplenism, electrolyte and water balance, radioiodine studies, the Kveim test, C-reactive protein, and plasma acetone in diabetes.

Modern Trends in Blood Diseases. By John F. Wilkinson, M.D. Price, $12.00. Pp. 359, with 92 illustrations. Paul B. Hoeber, Inc. (Medical Book Department of Harper & Brothers), 49 E. 33d St., New York, 1955.

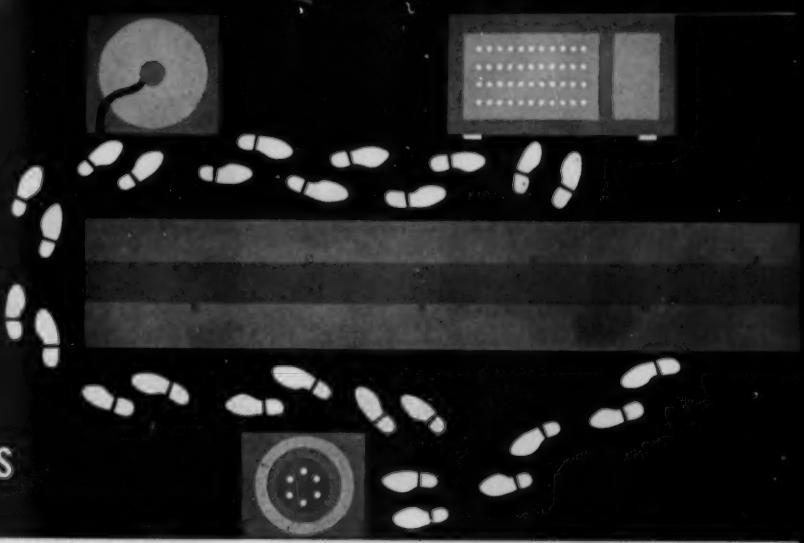
This is not a textbook of hematology but a report on the more important investigations dealing with diseases of the blood and blood-forming organs. Selection has been made from areas in which there has been considerable progress in the understanding of the etiology, diagnosis, and treatment. Well-known clinicians and scientists, distinguished both in the United States and in Great Britain, have contributed chapters on subjects with which they have been closely associated.

Early chapters show the integration of early signs and symptoms that exists between diseases of the blood-forming organs and other systems, including bone, skin, and the fundus of the eye. There is consideration of the advances in understanding and treating the hemolytic anemias, chronic and acute leukemias, and the reticuloses. Pediatric hematology and immunohematology are included, with attention to the newer aspects of diagnosis, etiology, and treatment. Recent work with anticoagulant substances for the control of thrombosis is combined with a discussion of some of the more important diagnostic techniques. The problems of pigment formation and clinical conditions associated with disturbances of these mechanisms are discussed. Progress is reported in attempts to elucidate factors concerned with iron absorption and utilization in iron-deficiency anemias.

This volume will be particularly helpful to those actively working in hematology, as a guide to present trends in a rapidly developing field.

Collagen Diseases. Volume II. By John H. Talbott, M.D., and R. Moleres Ferrandis, M.D. Price, $6.50. Pp. 232, with 30 black and white illustrations and 16 color plates. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1956.

In this monograph the authors have gathered together most of the facts and concepts concerning the diseases of connective tissue. They have dealt specifically with systemic lupus erythematosus, polyarteritis, dermatomyositis, systemic scleroderma, and thrombotic thrombocytopenic purpura. As Dr. Talbott says in the preface, this work represents "the culmination of twenty years of sporadic awareness of the need for a concise monograph on the disorders described herein." The 540 references represent the extensiveness of the study. Each disease process is considered from the aspects of historical concepts, incidence, etiology and pathogenesis, pathology, clinical findings, diagnosis, clinical course, and treatment. The monograph is well printed and contains numerous photographs of lesions, x-ray findings, and sixteen colored plates, which are reproduced by permission of Sharp & Dohme, Division of Merck & Co., Inc. Students of disease who are interested particularly in these types of abnormalities will find here in a condensed form the principal ideas concerning these processes.



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